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## (30)Priority

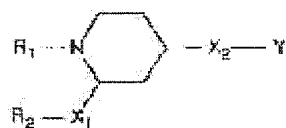
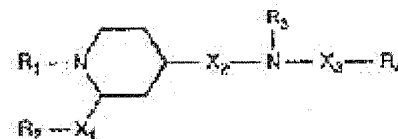
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## (54) 1-ACYLPIPERIDINE COMPOUND

## (57)Abstract:

PURPOSE: To provide a new metabolically stable compound useful for the treatment of diseases pertaining substance P, such as pain, central nervous system diseases, inflammation diseases, hypertension, or the like, as a substance-P- antagonistic agent.

CONSTITUTION: This compound is a compound represented by formula I, (wherein R1 is an aralkyl, aroyl, or the like; R2 is a cycloalkyl, aryl, or the like; R3 is H, an alkyl, or the like; R4 is an aryl or heteroaryl; X1 is methylene, ethylene, or the like; or a salt and/or a solvate X2 is an alkylene, carbonyl, or the like; and X3 is carbonyl, an oxo-lower alkylene, or the like) or a salt thereof, such as (2R, 4S)-2-benzyl-1-[3,5-bis-(trifluoromethyl)benzoyl]-N-(4-quinolylmethyl)-4-piperidinamine. The compound is obtained by, for example, condensing a compound represented by formula II, (wherein Y1 is -N(R3)-H) and a compound represented by formula Y2-X3-R4, [wherein Y2 is (reactive esterified) hydroxyl, or the like] in a solvent in the presence of a condensing agent, such as pyridine, or the like.



## LEGAL STATUS

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\* NOTICES \*

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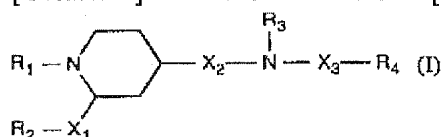
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## CLAIMS

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[Claim(s)]

[Claim 1] General formula I: [Formula 1]



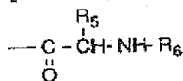
The aralkyl, aryloxy alkyl by which R<sub>1</sub> may be permuted among [ top type, A hetero aralkyl, aroyl, hetero aroyl, cycloalkyl carbonyl, [ whether they are aryl alkanoyl, hetero aryl alkanoyl, aryl alkoxy carbonyl, or an aryl carbamoyl group and ] Or it is the acyl group of the alpha-amino acid which may be carried out N-permutation by carbamoyl-low-grade alkanoyl. or low-grade alkanoyl -- R<sub>2</sub> It is the aryl or the hetero aryl group which has permuted [ cycloalkyl or ]. R<sub>3</sub> Or it is the alkanoyl or the ARUKE noil radical which may be permuted by the carboxyl

esterified or amidated. or it is hydrogen, alkyl, and carbamoyl -- or carboxyl -- R4 It is the hetero aryl group by which have been hydrogenated [ the aryl which may be permuted, or ] selectively. X1 It is the hydroxy methylene group by which have been etherified [ methylene, ethylene, direct coupling, the carbonyl group by which have been ketal-ized, or ]. X2 It is alkylene, carbonyl, or direct coupling, and is X3. Carbonyl, oxo--low-grade alkylene, oxo-(aza-)-low-grade alkylene By or the carboxyl which may be esterified or amidated by phenyl by hydroxymethyl Or 1-acyl piperidine compound expressed by] which is the alkylene group which may be permuted in a high order by the hydroxyl from an alpha position or its salt.

[Claim 2] R1 It is unsubstituted or sets for a phenyl component. By low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, phenyl - permuted by trifluoromethyl, It is a diphenyl -, naphthyl -, or fluorenyl-low-grade alkyl group and unsubstituted, or sets for a phenyl component. With a halogen And/or, the phenoxy-low-grade alkyl group permuted by thoria ZORIRU, The hetero aryl-low-grade alkyl group which has the aza--hetero aryl group which is 6 members as a hetero aryl group, is a monocycle type, or is a 2 ring type, and consists of six membered-rings, 5, or 6 membered-rings, Are unsubstituted or by low-grade alkyl by low-grade ARUKOKISHI By G low-grade alkylamino with the hydroxyl with a halogen It is noil or the cycloalkyl carbonyl group of 3 - 8 member, and unsubstituted, or sets for a phenyl component. cyano \*\* -- and/or, the benzoyl permuted by trifluoromethyl, naphthoyl, and full -- me -- by low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, the phenyl - or diphenyl-low-grade alkanoyl radical permuted by trifluoromethyl, The hetero aryl-low-grade alkanoyl radical which has the aza--hetero aryl which is 6 members as a hetero aryl group, is a monocycle type, or is a 2 ring type or a 3 ring type, and consists of six membered-rings, one piece, or two 5 or 6 membered-rings, It is unsubstituted or sets for a phenyl component. By low-grade alkyl by low-grade ARUKOKISHI By G low-grade alkylamino, with a halogen, and/or, the phenyl-low-grade alkoxy carbonyl or N-phenylcarbamoyl radical permuted by trifluoromethyl, Or it is the acyl group of the alpha-amino acid which may be carried out N-permutation by carbamoyl-low-grade alkanoyl. or -- as a peptide configuration unit -- nature -- existing -- and low-grade alkanoyl -- R2 Whether it is cycloalkyl of 5 - 7 member, or it is unsubstituted by or the low-grade alkyl combined in aromatic series By low-grade ARUKOKISHI, with a halogen, and/or, the phenyl permuted by trifluoromethyl, It is the monocycle type aza--hetero aryl group of naphthyl or 6 members, and is R3. Hydrogen, Low-grade alkyl, carbamoyl, low-grade alkanoyl, and carboxy-low-grade alkanoyl or carboxy-low-grade ARUKE noil, Low-grade alkoxy carbonyl-low-grade alkyl, carbamoyl-low-grade alkanoyl, N-Monod or N, and N-G low-grade alkyl carbamoyl-low-grade alkanoyl, It is N-cycloalkyl carbamoyl-low-grade alkanoyl or N-phenylcarbamoyl-low-grade alkanoyl, and is R4. Are unsubstituted or by or low-grade alkyl low-grade ARUKOKISHI -- a halogen -- and/or, it being the phenyl permuted by trifluoromethyl, naphthyl, a pyridyl radical, or

unsubstituted, or by low-grade alkyl And/or, C-permutation of is done by trifluoromethyl and N-permutation is carried out by the case by low-grade alkanoyl. low-grade ARUKOKISHI -- a halogen -- And it is the hetero aryl group which consists of Monod of 5 which may be hydrogenated selectively, or 6 members, G aza-- or an OKISA-hetero aryl group, and the aryl group of 6 members. X1 By methylene, ethylene, and low-grade alkanol, or the carbonyl group which may be ketal-ized by low-grade alkane diol, The hydroxy methylene group which may be etherified by low-grade alkanol, Or it is direct coupling and is X2. They are carbonyl, low-grade alkylene, or direct coupling. And X3 Carbonyl, oxo--low-grade alkylene, oxo-(aza)-low-grade alkylene, Or about N atom, 1, 2, or in existing, it sets to the 3rd place. or -- or it is unsubstituted -- or phenyl -- by carboxyl low-grade alkoxy carbonyl -- carbamoyl -- N-Monod or N, and N-G low-grade alkyl carbamoyl -- or the compound of the formula I according to claim 1 which is the low-grade alkylene group permuted by hydroxymethyl or its salt.

[Claim 3] R1 It is unsubstituted or sets for a phenyl component. By low-grade alkyl low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, phenyl - or diphenyl-C1-C4 permuted by trifluoromethyl alkyl -- Phenoxy-C1-C4 which is unsubstituted or was permuted with the halogen in the phenyl component Alkyl, Or thoria ZORIRU -, pyridyl -, or kino RINIRU-C1-C4 Are alkyl and unsubstituted or by or low-grade alkyl low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, it being unsubstituted [ which were permuted by trifluoromethyl / the benzoyl and unsubstituted ], or by low-grade alkyl low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, it being unsubstituted [ which were permuted by trifluoromethyl / the naphthoyl and unsubstituted ], or by low-grade alkyl low-grade ARUKOKISHI -- a halogen -- and/or, it being the pyridyl carbonyl permuted by trifluoromethyl or KINORI nil carbonyl, and unsubstituted, or by low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, the cycloalkyl carbonyl of 5 permuted by trifluoromethyl - 7 members, It is unsubstituted or sets for a phenyl component. By low-grade alkyl by low-grade ARUKOKISHI G low-grade alkylamino -- a halogen -- and/or, phenyl - or diphenyl-C1-C4 permuted by trifluoromethyl alkanoyl -- or it is unsubstituted -- or a phenyl component -- setting -- low-grade alkyl -- low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, N-phenylcarbamoyl which may be permuted by trifluoromethyl or radical [ of Formula Ia ]: -- [Formula 2]



(Among a top type, R5 is hydrogen and unsubstituted or by the hydroxyl) By the phenyl in which a hydroxy permutation may be carried out by amino by mercapto carboxyl -- carbamoyl - - or C1-C4 permuted by ureido It is alkyl. R6 [ and ] C2-C7 it is alkanoyl -- it is -- or [ whether R2 is cycloalkyl of 5 - 7 member, or that it is unsubstituted ] -- or C1-C4 combined in aromatic series By alkyl C1-C4 By ARUKOKISHI, with a halogen, and/or, phenyl permuted by

trifluoromethyl, It is naphthyl or a pyridyl radical and is R3. Hydrogen and C1-C7 Alkyl, Carbamoyl and C2-C7 Alkanoyl and carboxy-C1-C4 Alkanoyl or carboxy-C2-C4 It is ARUKE noil and is R4. It is unsubstituted or is C1-C4. By alkyl C1-C4 By ARUKOKISHI, with a halogen, and/or, phenyl or naphthyl permuted by trifluoromethyl, Or unsubstituted pyridyl, benzofuranyl one, the indolyl, 2, 3-dihydroindolyl, They are benzimidazolyl, quinolyl or 1, 2 and 3, and 4-tetrahydro kino RINIRU. X1 Methylene, hydroxy methylene, and C1-C4 Alkoxy methylene, Carbonyl and G C1-C4 They are alkoxy methylene or direct coupling. X2 C1-C7 They are alkylene, carbonyl, or direct coupling. And X3 Carbonyl and C1-C4 Alkylene and carboxy-C1-C4 Alkylene, C1-C4 Alkoxy carbonyl-C1-C4 Alkylene and carbamoyl-C1-C4 Alkylene or hydroxymethyl-C1-C4 The compound of the formula I according to claim 1 which is alkylene, or its salt.

[Claim 4] R1 or it is unsubstituted -- or C1-C4 alkyl -- C1-C4 ARUKOKISHI -- a halogen -- and/or, the benzoyl, the naphthoyl, or phenyl-C1-C4 permuted by trifluoromethyl alkanoyl -- it is -- or unsubstituted pyridyl carbonyl or KINORI nil carbonyl -- it is -- or radical [ of Formula Ia ]: -- [Formula 3]



(Among a top type, R5 is hydrogen and unsubstituted or by the hydroxyl) By the phenyl in which a hydroxy permutation may be carried out by amino by mercapto carboxyl -- carbamoyl - - or C1-C4 permuted by ureido It is alkyl. R6 [ and ] C2-C7 it is alkanoyl -- it is -- or [ whether R2 is cycloalkyl of 5 - 7 member, or that it is unsubstituted ] -- or C1-C4 combined in aromatic series By alkyl C1-C4 By ARUKOKISHI, with a halogen, and/or, phenyl permuted by trifluoromethyl, It is naphthyl or a pyridyl radical and is R3. Hydrogen and C1-C7 Alkyl, Carbamoyl and C2-C7 Alkanoyl and carboxy-C1-C4 Alkanoyl or carboxy-C3-C5 It is ARUKE noil and is R4. It is unsubstituted or is C1-C4. By alkyl C1-C4 By ARUKOKISHI, with a halogen, and/or, phenyl or naphthyl permuted by trifluoromethyl, Or it is pyridyl, benzofuranyl one, the indolyl, unsubstituted benzimidazolyl, or unsubstituted quinolyl. X1 Methylene, hydroxy methylene, and C1-C4 Alkoxy methylene, Carbonyl and G C1-C4 They are alkoxy methylene or direct coupling. X2 is C1-C7. They are alkylene, carbonyl, or direct coupling. And X3 Carbonyl and C1-C4 Alkylene and carboxy-C1-C4 Alkylene, C1-C4 Alkoxy carbonyl-C1-C4 Alkylene and carbamoyl-C1-C4 Alkylene or hydroxymethyl-C1-C4 The compound of the formula I according to claim 1 which is alkylene, or its salt.

[Claim 5] R1 It is unsubstituted or is C1-C4. By alkyl, it is C1-C4. By ARUKOKISHI a with an atomic number of 35 or less halogen -- and/or, trifluoromethyl -- a single permutation or the benzoyl carried out 2 \*\*\*\*s -- Or unsubstituted naphthoyl or unsubstituted phenyl-C1-C4 It is alkanoyl and is R2. It is unsubstituted or is C1-C4. By alkyl C1-C4 ARUKOKISHI -- a with an atomic number of 35 or less halogen -- and/or, trifluoromethyl -- a single permutation or the

phenyl carried out 2 \*\*\*\*s -- Or it is unsubstituted pyridyl and is R3. Hydrogen and C1-C4 Alkyl, carbamoyl, or C2-C7 It is alkanoyl, and R4 is unsubstituted, or it is C1-C4. By alkyl C1-C4 ARUKOKISHI -- a with an atomic number of 35 or less halogen -- and/or, trifluoromethyl -- a single permutation or the phenyl carried out 2 \*\*\*\*s -- Or unsubstituted naphthyl, pyridyl, benzofuranyl one, indolyl, It is benzimidazolyl or quinolyl, X1 is methylene, hydroxy methylene, carbonyl, or direct coupling, and it is X2. It is direct coupling and is X3. C1-C4 The compound of the formula I according to claim 1 which is alkylene, or its salt.

[Claim 6] R1 It is unsubstituted or is C1-C4. By alkyl, it is C1-C4. By ARUKOKISHI a with an atomic number of 35 or less halogen -- and/or, trifluoromethyl -- a single permutation or the benzoyl carried out 2 \*\*\*\*s -- or unsubstituted naphthoyl -- it is -- R2 And/or, they are a single permutation or the phenyl carried out 2 \*\*\*\*s by trifluoromethyl. or it is phenyl -- or a with an atomic number of 35 or less halogen -- R3 It is hydrogen and is R4. It is unsubstituted kino RINIRU and is X1. It is methylene and is X2. It is direct coupling and is X3. C1-C4 The compound of the formula I according to claim 1 which is alkylene, or its salt.

[Claim 7] (2R\* and 4S\*)-2-benzyl-1-[3 and 5-screw-(trifluoromethyl) benzoyl]-N-(4-quinolyl methyl)-4-piperidine amine or its salt.

[Claim 8] 2R, (4S)-, -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine, or its salt.

[Claim 9] () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (2-naphthoyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3-trifluoromethyl benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dimethoxybenzoyl)-N- (4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(1-naphthoyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\*, 4S\*) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (2-KINORI nil carbonyl)-N- (4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (4-chlorophenyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\*, 4S\*) -2-benzyl-1-(benzyloxycarbonyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(2-phenylethyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(2-naphthyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(4-quinolyl methyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(2, 4-dichloro benzyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(2 and 2-diphenyl ethyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(phenylcarbamoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(diphenyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(2-pyridyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (4-pyridyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(2, 3-diphenyl propionyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- {(3S)- Carbonyl}-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3-methoxy

benzoyl)-N-(2, 3, 4, 9 - Tetrahydro-1H-[3 and 4-pyrid b] Indore-3-IRU) (4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3-N and N-dimethylamino benzoyl)-N- (4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(cis-, cis- - 3, 5-dimethyl cyclohexyl carbonyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-[3, 5-screw Benzyl]-N- (Trifluoromethyl) (4-quinolyl methyl)-4-piperidine amine; (2S\* and 4R\*) -2-benzyl-1-[2-(5-chloro-1H- 1, 2, 4-triazole-1-IRU) phenoxy ethyl]-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- ((S)-phenyl alanyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-((R)-phenyl alanyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- () (S) -N-acetyl phenyl alanyl-N- (4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- () (R) -N-acetyl phenyl alanyl-N- (4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-[(S)-N-(4-carboxamide BUCHIROIRU) phenyl alanyl]-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- [ -- (R) -N-(4-carboxamide BUCHIROIRU) phenyl alanyl]-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-benzoyl-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3-chloro benzoyl)-N- (4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N- (4-quinolyl methyl)-N- (3-carboxamide propionyl)-4-piperidine amine; 2S and (R[ 4 ]) - or 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-phenethyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(3-quinolyl methyl)-4-piperidine amine;(R [ 2 ], 4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(2-quinolyl methyl)-4-piperidine amine; (2R) 4S-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-quinolyl methyl)-4-piperidine amine; 2R and (4S)- or R [ 2 ] and (R[ 4 ]) -2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-benzyl-4-piperidine amine;(2S, 4R)- or (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-benzyl-4-piperidine amine;(R [ 2 ], 4S)- or R [ 2 ] and (R [ 4 ]) -2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (4-pyridyl methyl)-4-piperidine amine; 2R and (4S)- or R [ 2 ] and (R[ 4 ]) -2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (3-pyridyl methyl)-4-piperidine amine; 2S and (R[ 4 ]) - or 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (4-quinolyl methyl)-4-piperidine amine; 2R and (4S)- or R [ 2 ] and (R[ 4 ]) -2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-phenethyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1-[3, 5-screw Benzoyl]-N-(4-quinolyl methyl)-4-piperidine amine; (2R, 4S) (Trifluoromethyl) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(2, 4-dichlorobenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(phenylacetyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (2 and 6-dichlorobenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine;(2R\* and 4S\*) -2-benzyl-1-(3, 5-dibromobenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(9-full me noil)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3-toluoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3-BUOMO benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3, 5-dihydroxybenzoyl)-N-(4-



quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(3-cyano benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(2-chloro benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-(4-chloro benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(9-fluorenyl)-N-(4-quinolyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N- (4-quinolyl methyl)-N-methyl-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl methyl)-N-cyclohexyl carbamoyl-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N- (4-quinolyl methyl)-N-phenylcarbamoyl-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(2-phenylethyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-[3, 5-screw Benzoyl]-N-(2-phenylethyl)-4-piperidine amine; (2R\* and 4S\*) (Trifluoromethyl) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(2-naphthoyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N-(3, 5-dimethylbenzoyl)-4-piperidine amine;(2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl carbonyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N-(3-indolyl carbonyl)-4-piperidine amine;(2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(2-indolyl carbonyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N- (5-methoxy-2-indolyl carbonyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(1-naphthoyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N-(phenylacetyl)-4-piperidine amine;(2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(2-methoxybenzyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N-[3- Indolyl methyl]-4-piperidine amine; (2R\* and 4S\*) (N-acetyl) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(2-[benzob] furanyl methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N- [ -- (3-methyl [benzob] thiophene-2-ylmethyl)-4-piperidine amine; (2R\* and 4S\*) -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(5-methoxy Indore-3-ylmethyl)-4-piperidine amine; (2R\*, 4S\*)) -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N-(3-indolyl methyl)-4-piperidine amine;(2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-phenylcarbamoyl-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dichlorobenzoyl)-N-diphenyl methyl-4-piperidine amine;(2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(3 4 - dihydro-2H-1-benzopyran-2-carbonyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (4-methoxy benzoyl)-N- (4-quinolyl methyl)-4-piperidine amine; (2R\*, 4S\*, and 1'R\*) -N-benzyl-1-(3, 5-dimethylbenzoyl)-2-(1'-hydroxy-1'-phenylmethyl)-4-piperidine amine; () [ 2R\*, 4S\*, ] [ 1'R\* ] -2-(1'-hydroxy-1'-phenylmethyl)-1- (3 and 5-dimethylbenzoyl)-N- (4-KINORI nil methyl)-4-piperidine amine; (2R\*, 4S\*, and 1'S\*)-1-(3, 5-dimethylbenzoyl)-2-(1'-hydroxy-1'-phenylmethyl)-N-(4-KINORI nil methyl)-4-piperidine amine; () [ 2R\*, 4S\*, ] [ 1'R\* ] -2-[1'-hydroxy-1'- Methyl]-1-(4-chlorophenyl) (3 and 5-dimethylbenzoyl)-N- (4-KINORI nil methyl)-4-piperidine amine; (2R\*, 4S\*, and 1'S\*)-1-(3, 5-dimethylbenzoyl)-2-[1'-hydroxy-1'-(4-chlorophenyl) methyl]-N-(4-KINORI nil methyl)-4-piperidine amine; () [ 2R\*, 4S\*, ] [ 1'S\* ] -1- 3 -- 5-dimethylbenzoyl-2-[1'-hydroxy-

1'- Methyl]-N-(4-KINORI nil methyl)-4-piperidine amine; (2R\* and 4S\*) (3, 4-dichlorophenyl) -N-benzyl-1-(3, 5-dimethylbenzoyl)-2-benzoyl-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2- (4-chloro benzyl)-1- (3 and 5-dimethylbenzoyl)-N- (4-KINORI nil methyl)-4-piperidine amine; (2R\* and 4S\*) -2-(3, 4-dichloro benzyl)-1-(3, 5-dimethylbenzoyl)-N-(4-KINORI nil methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -2- (3 and 5-dichloro benzyl)-1- (3 and 5-dimethylbenzoyl)-N-(4-KINORI nil methyl)-4-piperidine amine;(2R\* and 4S\*)-1-(3, 5-dimethylbenzoyl)-2-phenyl-N-(4-KINORI nil methyl)-4-piperidine amine; () [ 2R\*, ] [ 4S\* ] -1- (3 and 5-dichlorobenzoyl)-2-phenyl-N-(4-KINORI nil methyl)-4-piperidine amine;(2R\* and 4S\*)-1-(1-naphthoyl)-2-phenyl-N-(4-KINORI nil methyl)-4-piperidine amine; -- or () [ 2R\*, ] [ 4S\* ] -1-(3, 5-dimethylbenzoyl)-2-(1-naphthyl)-N-(4-KINORI nil methyl)-4-piperidine amine or its salt permitted on a remedy in each  
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[Claim 10] () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-benzyl-N-carbamoyl-4-piperidine amine;(R [ 2 ], 4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(3-phenylpropyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (3-phenylpropyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-methoxybenzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-methoxybenzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2-methoxyphenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2-methoxyphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2-methoxyphenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2-methoxyphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-trifluoro methylbenzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-trifluoro methylbenzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(2-trifluoro methylphenyl) ethyl]-4-piperidine amine; (2-trifluoro methylphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2-trifluoro methylphenyl) propyl]-4-piperidine amine; (2-trifluoro methylphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (3-trifluoro methylbenzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (3-trifluoro methylbenzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(3-trifluoro methylphenyl) ethyl]-4-piperidine amine; (3-trifluoro methylphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(3-trifluoro methylphenyl) propyl]-4-piperidine amine; (3-trifluoro methylphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (4-trifluoro methylbenzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (4-

trifluoro methylbenzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(4-trifluoro methylphenyl) ethyl]-4-piperidine amine; (4-trifluoro methylphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(4-trifluoro methylphenyl) propyl]-4-piperidine amine; (4-trifluoro methylphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 3-dimethoxy benzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 3-dimethoxy benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- -2-benzyl-1- (2, 3-dimethoxy phenyl) ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)- N-[2-(2, 3-dimethoxy phenyl) ethyl]-4-piperidine amine; (2R, 4S) -- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2, 3-dimethoxy phenyl) propyl]-4-piperidine amine; (2, 3-dimethoxy phenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 4-dimethoxy benzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 4-dimethoxy benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(2, 4-dimethoxy phenyl) ethyl]-4-piperidine amine;(2S, 4S)-2-benzyl -1 - (3, 5-dimethylbenzo) IRU-N-[2- Ethyl]-4-piperidine amine; (2R, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2, 4-dimethoxy phenyl) propyl]-4-piperidine amine; (2, 4-dimethoxy phenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- -2-benzyl-1- (2, 4-dimethoxy phenyl) propyl]-4-piperidine amine; (2R, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(2, 5-dimethoxy benzyl)-4-piperidine amine; (2S, 4S) -- (3 and 5-dimethylbenzoyl)-N- (2 and 5-dimethoxy benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- -2-benzyl-1- (2, 5-dimethoxy phenyl) ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)- N-[2-(2, 5-dimethoxy phenyl) ethyl]-4-piperidine amine; (2R, 4S) -- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2, 5-dimethoxy phenyl) propyl]-4-piperidine amine; (2, 5-dimethoxy phenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 6-dimethoxy benzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 6-dimethoxy benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- -2-benzyl-1- (2, 6-dimethoxy phenyl) ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)- N-[2-(2, 6-dimethoxy phenyl) ethyl]-4-piperidine amine; (2R, 4S) -- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2, 6-dimethoxy phenyl) propyl]-4-piperidine amine; (2, 6-dimethoxy phenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 3-methylene dioxy benzyl)-4-piperidine amine;(2S, 4S)-2-benzyl-1- (3, 5-dimethylbenzoyl)-N-(2, 3-methylene dioxy benzyl)-4-piperidine amine;(R [ 2 ], 4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(2, 3-methylenedioxyphenyl) ethyl]-4-piperidine amine; (2, 3-

methylenedioxyphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2, 3-methylenedioxyphenyl) propyl]-4-piperidine amine; (2, 3-methylenedioxyphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2 and 4-methylene dioxy benzyl)-4-piperidine amine;(2S, 4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(2, 4-methylene dioxy benzyl)-4-piperidine amine;(R [ 2 ], 4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(2, 4-methylenedioxyphenyl) ethyl]-4-piperidine amine; (2, 4-methylenedioxyphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2S, 4S) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3-(2, 4-methylenedioxyphenyl) propyl]-4-piperidine amine; (2, 4-methylenedioxyphenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-2-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-2-ylmethyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-3-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-3-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Quinoline-2-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Quinoline-3-ylmethyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-chloro benzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (2-chloro benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (2-chlorophenyl) 2S and (4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[2-(2-chlorophenyl) ethyl]-4-piperidine amine;(R [ 2 ], 4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-[3 - (2-clo) ROFENIRU propyl]-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (2-chlorophenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (3-chloro benzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (3-chloro benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (3-chlorophenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (3-chlorophenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (3-chlorophenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (3-chlorophenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (4-chloro benzyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (4-chloro benzyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (4-chlorophenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[2- Ethyl]-4-piperidine amine; (4-chlorophenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (4-chlorophenyl) 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-[3- Propyl]-4-piperidine amine; (4-chlorophenyl) R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- -2-benzyl-1- (4-methoxy North America Free Trade Agreement-1-ylmethyl)-4-piperidine amine; (2S, 4S) -2-

benzyl-1-(3, 5-dimethylbenzoyl)-N-(4-methoxy North America Free Trade Agreement-1-ylmethyl)-4-piperidine amine; (2R, 4S) -- (3 and 5-dimethylbenzoyl)-N- (3 and 4-ethylene dioxy benzyl)-4-piperidine amine;(2S, 4S)-2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(3, 4-ethylene dioxy benzyl)-4-piperidine amine;(R [ 2 ], 4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-2-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-2-ylmethyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-3-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Indore-3-ylmethyl)-4-piperidine amine; R [ 2 ] and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N- (Quinoline-2-ylmethyl)-4-piperidine amine; 2S and (4S)-2-benzyl-1- (3 and 5-dimethylbenzoyl)-N-

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#### \* NOTICES \*

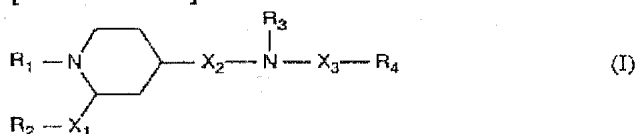
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1. This document has been translated by computer. So the translation may not reflect the original precisely.
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#### DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001] The new 1-acyl piperidine compound whose this invention is a general formula I: It is [Formula 15].



The aralkyl, aryloxy alkyl by which R<sub>1</sub> may be permuted among [ top type, A hetero aralkyl, aroyl, hetero aroyl, cycloalkyl carbonyl, [ whether they are aryl alkanoyl, hetero aryl alkanoyl, aryl alkoxy carbonyl, or an aryl carbamoyl group and ] Or it is the acyl group of the alpha-amino acid which may be carried out N-permutation by carbamoyl-low-grade alkanoyl. or low-grade alkanoyl -- R<sub>2</sub> It is the aryl or the hetero aryl group which has permuted [ cycloalkyl or ]. R<sub>3</sub> Or it is the alkanoyl or the ARUKE noil radical which may be permuted by the carboxyl

esterified or amidated. or it is hydrogen, alkyl, and carbamoyl -- or carboxyl -- R4 It is the hetero aryl group by which have been hydrogenated [ the aryl which may be permuted, or ] selectively. X1 It is the hydroxy methylene group by which have been etherified [ methylene, ethylene, direct coupling, the carbonyl group by which have been ketal-ized, or ]. X2 It is alkylene, carbonyl, or direct coupling, and is X3. Carbonyl, oxo--low-grade alkylene, oxo-(aza-)-low-grade alkylene By or the carboxyl which may be esterified or amidated by phenyl by hydroxymethyl Or] which is the alkylene group which may be permuted in a high order by the hydroxyl from an alpha position and the preparation approach of those compounds of salt; this invention; it is related with those utilization as a remedy active substance at the drugs; list containing them.

[0002] or said aryl, aroyl, aryl alkanoyl, hetero aryl, and a hetero aroyl radical are unsubstituted -- or -- for example, the low-grade alkyl combined in aromatic series -- low-grade ARUKOKISHI -- a halogen -- and/or, trifluoromethyl -- a permutation, for example, a single permutation, two permutations or three permutations, especially a single permutation -- or 2 \*\*\*\*s may be carried out. Aryl, an aralkyl, aryloxy alkyl, cycloalkyl carbonyl, and an aroyl radical are a single permutation, two permutations, for example, 3-permutation, or 3 and 5, as preferably mentioned above. - It permutes two times and; hetero aryl, a hetero aralkyl, hetero aryl alkanoyl, and a hetero aroyl radical are unsubstituted preferably. An aralkyl is the phenyl - or diphenyl-low-grade alkyl which may be permuted in for example, a phenyl component or a naphthyl component.

[0003] Aryloxy-low-grade alkyl is the phenoxy-low-grade alkyl which may be permuted for example, in a phenyl component. Hetero alkyl is 6 members as for example, a hetero aryl group, is a monocycle type, or is a 2 ring type, and is a hetero aryl-low-grade alkyl group which has the aza--hetero aryl which consists of six membered-rings, 5, or 6 membered-rings.

[0004] aroyl -- for example, benzoyl which may be permuted, for example, benzoyl, 3-low-grade alkyl -, 3-low-grade alkoxy -, 3-halogeno -, 3-dimethylamino -, 3, 5-JI low-grade alkyl, 3, and 5-JI -- low-grade -- they are alkoxy \*\*3 and 5-dihalogeno or 3, 5-ditrifluoromethyl-benzoyl or the naphthoyl that may be permuted by the second, for example, 1-, and 2-naphthoyl. Hetero aroyl is for example, 6 members, is a monocycle type, or is a 2 ring type, and is the aza--hetero aroyl which consists of six membered-rings, 5, or 6 membered-rings, for example, pyridyl carbonyl, and KINORI nil carbonyl.

[0005] Cycloalkyl carbonyl is cycloalkyl carbonyl of 3 which may be permuted - 8 member, especially 5 - 7 member, for example, cyclohexyl carbonyl, and 3-low-grade alkyl -, 3-low-grade alkoxy -, 3-halogeno -, 3-dimethylamino -, 3, 5-JI low-grade alkyl -, 3, 5-JI low-grade alkoxy -, 3, and 5-dihalogeno - or 3, and 5-ditrifluoromethyl-cyclohexyl carbonyl, for example.

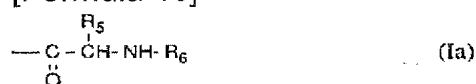
[0006] Aryl alkanoyl means the phenyl - or diphenyl-low-grade alkanoyl which may be permuted for example, in a phenyl component. Hetero aryl alkanoyl is 6 members as for

example, a hetero aryl group, is a monocycle type, or is a 2 ring type, and is hetero aryl-low-grade alkanoyl which has the aza--hetero aryl which consists of six membered-rings, 5, or 6 membered-rings. Aryl carbamoyl means N-phenylcarbamoyl which may be permuted for example, in a phenyl component.

[0007] especially the acyl group of the alpha-amino acid which may be formed into N-alkanoyl is guided from the amino acid which exists naturally as a peptide configuration unit -- having -- and the formation 7 of low-grade alkanoyl, for example, N-C2-C, being alkanoyl-ized -- it is -- for example, acetyl -- a propionyl -- the butyryl -- or pivaloyl may permute The example is :

[0008] which is the radical of Formula Ia.

[Formula 16]



[0009] The inside of a top type, and R5 By hydrogen or the hydroxyl, by amino By the phenyl in which a hydroxy permutation may be carried out by mercapto Or it is the low-grade alkyl group which may be permuted by ureido. carboxyl -- carbamoyl -- For example, C1-C4 An alkyl group, for example, methyl, isopropyl, isobutyl, The second butyl, hydroxymethyl, mercaptomethyl, 2-methyl mercapto ethyl, 3-ureido propyl, 4-amino butyl, carboxymethyl, carbamoyl methyl, It is 2-carboxy ethyl, 2-carbamoyl ethyl, benzyl, or 4-hydroxybenzyl, and is R6. Low-grade alkanoyl 7, for example, C2-C, They are alkanoyl, for example, acetyl, a propionyl, the butyryl, or pivaloyl. However, it can also be the acyl group, for example, the prolyl, TORIPUTOFANIRU, or hysteries CHIJINIRU of the heterocycle type alpha-amino acid which exists naturally as a configuration unit of a peptide.

[0010] cycloalkyl -- for example, the cycloalkyl of 5 - 7 member -- for example [ especially ], it is cyclopentyl or cycloheptyl cyclohexyl or the second. aryl -- for example, phenyl -- or -- especially -- R4 \*\*\*\*\* -- it is naphthyl. Hetero aryl For example, the monocycle type aza--hetero aryl of 6 members, for example, pyridyl, R4 [ or ] It is the hetero aryl which consists of mono-aza-- of 5 members which may be hydrogenated especially selectively, or 6 members, diaza - or an OKISA-hetero aryl group, and the aryl group of 6 members. \*\*\*\*\* -- For example, benzofuranyl one, for example, benzofuran-2-IRU, or -3-IRU, The indolyl, for example, Indore-2-IRU, or -3-IRU, 2, the 3-dihydroindolyl, For example, it is 2 and 3-dihydroIndore-2-IRU or -3-IRU, benzimidazolyl, for example, benzimidazole-2-IRU, quinolyl, for example, quinoline-4-IRU, or 1, 2 and 3, and 4-tetrahydroquinoline-4-IRU.

[0011] As hetero aryl of the hetero aryl-low-grade alkanoyl which has the aza--hetero aryl which is 6 members, is a monocycle type, is a 2 ring type, and consists of six membered-rings, 5, or 6 membered-rings For example, corresponding hetero aryl-C1-C4 Alkanoyl, for example, 2-pyridyl, - or 4-pyridyl acetyl, 2, 3, 4, 9 - It is tetrahydro-1H-[3 and 4-pyrid b] Indore-3-yl-carbonyl.

[0012] Especially alkyl is low-grade alkyl and especially; alkylene is low-grade alkylene. It is fatty alcohol or dialcohol, for example, the ketal-ized carbonyl group is ketal-ized by low-grade alkanol or low-grade alkane diol, for example, is G low-grade alkoxy methylene or low-grade alkylene dioxy methylene.

[0013] It is fatty alcohol, for example, especially the etherified hydroxy methylene is etherified by low-grade alkanol, and is for example, low-grade alkoxy methylene. The carboxyl which may be esterified or amidated is carboxyl, low-grade alkoxy carbonyl, carbamoyl, or N-Monod or N, and N-G low-grade alkyl carbamoyl.

[0014] By carboxyl, or the alkanoyl or the ARUKE noil radical which may be permuted by the carboxyl esterified or amidated (For example, low-grade alkanoyl 7, for example, C2-C, alkanoyl, for example, acetyl) A propionyl, the butyryl or pivaloyl, carboxy-low-grade alkanoyl, For example, carboxy-C3-C7 Alkanoyl, for example, succinoyl, A GURUTA roil, horse mackerel POIRU, or carboxy-low-grade ARUKE noil, For example, carboxy-C3-C5 ARUKE noil, for example, MAREIRU, It is FUMAROIRU or a tart roil, and carboxy can be esterified or amidated here. (For example, the low-grade alkoxy carbonyl 4, for example, C1-C, alkoxy carbonyl) For example, methoxy - or ethoxycarbonyl, carbamoyl, or N-Monod or N, and N-G low-grade alkyl carbamoyl, For example, N-Monod or N, and N-G C1-C4 It can be alkyl carbamoyl, for example, N-methyl, or N, and N-dimethyl carbamoyl.

[0015] The low-grade alkylene permuted by the hydroxyl in the high order from the alpha position is hydroxylated in the 2nd place for example, about N atom. hydroxymethyl -- or the low-grade alkylene permuted by the carboxyl which may be esterified or amidated -- for example, N atom -- being related -- 1, 2, or the case where it exists -- the 3rd place -- setting -- carboxyl -- low-grade alkoxy carbonyl -- carbamoyl -- N-Monod or N, and N-G low-grade alkyl carbamoyl -- or hydroxymethyl permutes.

[0016] It is interpreted as seven or less the radicals and compounds of a low class being what has four or less carbon atoms (C atom) preferably in the above and the following, for example. low-grade alkyl -- for example, C1-C7 alkyl -- desirable -- C1-C4 although it is ethyl, propyl, isopropyl, or butyl alkyl especially methyl, or the second -- isobutyl, the second butyl, tertiary butyl, or C5-C7 They can also be alkyl, for example, pentyl, hexyl, or a heptyl radical. low-grade alkylene -- for example, C1-C7 alkylene -- desirable -- C1-C4 It is alkylene, for example, methylene, ethylene, 1, 3-propylene, 1, and 4-butylene or 1, and 5-pentene.

[0017] The phenyl - or diphenyl-low-grade alkyl which may be permuted in a phenyl component is corresponding phenyl - or corresponding diphenyl-C1-C4. It is alkyl, for example, benzyl, 2, 4-dichloro benzyl, 3, 5-trifluoro methylbenzyl, 2-phenylethyl or 2, and 2-diphenyl ethyl. The phenyl - or diphenyl-low-grade alkanoyl which may be permuted in a phenyl component is corresponding phenyl - or diphenyl-C1-C4 alkanoyl, 2 [ for example, ], and 2-diphenyl acetyl or 2, and 3-diphenyl propionyl, for example.



[0018] the phenoxy-low-grade alkyl which may be permuted in phenyl -- for example, a halogen -- and/or, phenoxy-C1-C4 permuted by thoria ZORIRU It is alkyl, for example, 2-[2-(1H- 1, 2, 4-triazole-1-IRU)-4-chloro phenoxy] ethyl. It is 6 members as a hetero aryl group, is a monocycle type, it is a 2 ring type, and the hetero aryl-low-grade alkyl which has the aza--hetero aryl which consists of six membered-rings, 5, or 6 membered-rings is for example, pyridyl - or kino RINIRU-C1-C4 alkyl, for example, 4-KINORI nil methyl.

[0019] low-grade alkoxy \*\* 7, for example, C1-C, alkoxy \*\* -- desirable -- C1-C4 Although it is alkoxy \*\*, for example, methoxy, and ethoxy \*\* propyloxy, isopropyloxy, or butyloxy, they can also be isobutyloxy, the second butyloxy, the third butyloxy or pentyloxy one, hexyloxy one, or a heptyloxy radical. The atomic numbers of a halogen are 35 or less halogen, for example, chlorine, a fluorine, and also a bromine.

[0020] low-grade ARUKOSHI carbonyl -- for example, C1-C7 alkoxy carbonyl -- desirable -- C1-C4 Although it is alkoxy carbonyl, for example, methoxycarbonyl, ethoxycarbonyl, propyloxy carbonyl, isopropyloxy carbonyl, or butyloxy carbonyl, they can also be isobutyloxy carbonyl, the second butyloxy carbonyl, the third butyloxy carbonyl or pentyloxy carbonyl, hexyloxy carbonyl, or a heptyloxy carbonyl group.

[0021] N-low-grade alkyl carbamoyl -- for example, N-C1-C7 alkyl carbamoyl -- desirable -- N-C1-C4 Although it is alkyl carbamoyl, for example, methyl carbamoyl, ethyl carbamoyl, propyl carbamoyl, isopropyl carbamoyl, or butylcarbamoyl, they can also be isobutyl carbamoyl, the second butylcarbamoyl, the third butylcarbamoyl or pentyl carbamoyl, hexyl carbamoyl, or a heptyl carbamoyl group.

[0022] N and N-G low-grade alkyl carbamoyl For example, N and N-G C1-C7 alkyl carbamoyl, It is N and N-G C1-C4 preferably. Alkyl carbamoyl For example, N and N-dimethyl carbamoyl, N, and N-diethylcarbamoyl, Although it is N-ethyl-N-methyl carbamoyl, N, and N-dipropyl carbamoyl, N-methyl-N-propyl carbamoyl, N-isopropyl-N-methyl carbamoyl, or N-butyl-N-methyl carbamoyl N-isobutyl-N-methyl carbamoyl, the N-methyl-N-second butylcarbamoyl, They can also be the N-methyl-N-third butylcarbamoyl or, N-methyl-N-pentyl carbamoyl, N-hexyl-N-methyl carbamoyl, or an N-heptyl-N-methyl carbamoyl group.

[0023] The low-grade alkylene which is a high order and was permuted [ in / at least from omega / lower order ] by the hydroxyl from the alpha position is 1, 3-(2-hydroxy) propylene, 1, 4-(2-hydroxy) butylene, 1, 4-(3-hydroxy) butylene, 1, 5-(2-hydroxy) pentene, 1, and 5-(3-hydroxy) pentene or 1, and 5-(4-hydroxy) pentene. The low-grade alkylene permuted by carboxyl is carboxymethylene, 1- or 2-carboxy ethylene, 1, 3-(2-carboxy) propylene, 1, 4-(2-carboxy) butylene, 1, 4-(3-carboxy) butylene, 1, 5-(2-carboxy) pentene, 1, and 5-(3-carboxy) pentene or 1, and 5-(4-carboxy) pentene.

[0024] The low-grade alkylene permuted by low-grade alkoxy carbonyl For example, low-grade alkoxy carbonyl methylene, 1-, or 2-low-grade alkoxy carbonyl ethylene, 1, 3-(2-low-grade

alkoxy carbonyl) propylene, 1, 4-(2-low-grade alkoxy carbonyl) butylene, 1, 4-(3-low-grade alkoxy carbonyl) butylene, 1, 5-(2-low-grade alkoxy carbonyl) pentene, It is 1 and 5-(3-low-grade alkoxy carbonyl) pentene or 1, and 5-(4-low-grade alkoxy carbonyl) pentene. Here the low-grade alkoxy carbonyl of each \*\*\*\* For example, C1-C4 Alkoxy carbonyl, for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, or butoxycarbonyl is meant.

[0025] By carbamoyl, the low-grade alkylene permuted by N-Monod or N, and N-G low-grade alkyl carbamoyl especially by carbamoyl For example, carbamoyl methylene, 1-, or 2-carbamoyl ethylene, 1, 3-(2-carbamoyl) propylene, 1, 4-(2-carbamoyl) butylene, It is 1, 4-(3-carbamoyl) butylene, 1, 5-(2-carbamoyl) pentene, 1, and 5-(3-carbamoyl) pentene or 1, and 5-(4-carbamoyl) pentene.

[0026] The low-grade alkylene permuted by hydroxymethyl 2-hydroxy ethylidene, 2, 3-(1-hydroxy) propylene, 1, 3-(2-hydroxymethyl) propylene, 2, 4-(1-hydroxy) butylene, It is 1, 4-(2-hydroxymethyl) butylene, 1, 4-(3-hydroxymethyl) butylene, 1, 5-(2-hydroxymethyl) pentene, 1, and 5-(3-hydroxymethyl) pentene or 1, and 5-(4-hydroxymethyl) pentene.

[0027] Low-grade alkoxy methylene is C1-C4. They are alkoxy methylene, for example, methoxy methylene, ethoxy methylene, propyloxy methylene, or butyloxy methylene. G low-grade alkoxy methylene is G C1-C4. They are alkoxy methylene, for example, dimethoxy methylene, diethoxy methylene, dipropyl oxy-methylene, or dibutyl oxy-methylene.

[0028] 5 - 8 member especially low-grade alkylene dioxy methylene 5 or 1 of 6 members, 3-dioxa cyclo ARUKA-2-IRU, For example, 1, 3-dioxa cyclo swine-2-IRU, 1, 3-dioxa cyclo PENTA-2-IRU (1, 3-dioxolane-2-IRU), It is 1, 3-dioxacyclohexa-2-IRU (1, 3-dioxane-2-IRU) or 1, and 3-dioxa cyclo hepta--2-IRU.

[0029] The compound of Formula I has basicity or is R3. And/or, X3 Since it has both sexes when carboxyl permutes, in an acid addition salt and a suitable case, inner salt can be formed. the acid addition salt of the compound of Formula I -- for example, the remedy up with a suitable inorganic acid, for example, halide acid, a sulfuric acid, or a phosphoric acid -- it is an available salt, for example, a hydrochloride, the hydrobromate, a sulfate, a sulfuric-acid hydro acid salt, or phosphate, or they are a salt with aliphatic series, a suitable aromatic series sulfonic acid, or suitable N-permutation sulfamic acid, for example, a methansulfonic acid salt, a benzenesulfonic acid salt, a p-toluenesulfonic-acid salt, or N-cyclohexylsulfamic acid salt (cyclamate). It is also possible to use an unsuitable salt on a remedy isolation or for the purpose of purification. However, since only an available nontoxic salt is used on a therapy on a remedy, they are desirable.

[0030] The compound prepared according to this invention has an effective pharmacology property. Especially, they show remarkable antagonism to substance P, and show the spectrum of a typical property to a substance P antagonist. therefore, the compounds of Formula I and those remedy up -- an available salt -- the inside of a test tube -- the

concentration about 10micro mol / more than L -- H.Bittiger \*\* -- CibaFoundation Symposium 91 and cow retina in the radioreceptor assay of 196-199 (1982) Association of 3H-substance P is checked thoroughly. In in the living body, they are Andrews. When it reaches and measures in the lug of a guinea pig based on the laboratory procedure of Helme, Regul.Rept.25, and 267-275 (1989), it is about 0.01 mg/kg i.v. The vasodilatation induced by substance P is prevented from a dosage. : from which the following ED50 value was acquired in this model [0031] (2R\* and 4S\*)-2-benzyl-1-[3 and 5-bis(trifluoromethyl) benzoyl]-N-(4-quinolyl methyl)-4-piperidine amine (example 4):0.1 mg/kg iv;(R [ 2 ], 4S)- And (2R, 4R) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(4-quinolyl methyl)-4-piperidine-amine dihydrochloride (example 76): 1.0 mg/kg iv.

[0032] Furthermore, Lundberg et al., Proc.Nat.Acad.Sci.(USA) 80, and 1120-1124 If based on a laboratory procedure, the bronchospasm by which vagus nerve induction was carried out in the guinea pig will be prevented from the dosage of about 1.0 mg/kg i.v. This is Andrews. And the felicity to the therapy of the asthma of Helme, Regul.Rept.25, and 267-275 (1989) is pointed out. : from which the following ED50 value was acquired in this model [0033] (2R\* and 4S\*)-2-benzyl-1-[3 and 5-bis(trifluoromethyl) benzoyl]-N-(4-quinolyl methyl)-4-piperidine amine (example 4):1.0 mg/kg iv;(R [ 2 ], 4S)- And (2R, 4R) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(4-quinolyl methyl)-4-piperidine-amine dihydrochloride (example 76): 3.0 mg/kg iv.

[0034] the availability of those compounds to the therapy of the disease of a central nervous system -- for example, A.Vassout et al., Meeting on Substance P, and Worcester Mass (1990) following -- a gerbil -- setting -- icv it points out by the inhibitory action to behavior change induced by the applied substance P methyl ester -- having -- this compound -- about 10 mg/kg s.c. from -- about 30 mg/kg i.p. from -- and it has ED50 from about 100 mg/kg p.o.

[0035] Substance P is the undeca peptide of the length kinin group which exists naturally. It is produced in the body of mammalian and works as a neuropeptide in pharmacology. Substance P plays an important role in hypertension at the dyskinesia of a certain kind, for example, Parkinson's disease, and also an inflammation disease, for example, articular rheumatism, iritis and the conjunctivitis and the disease of respiratory organs, for example, asthma, the chronic bronchitis and the disease of a gastrointestinal system, for example, ulcerative colitis, Crohn's disease, and a list in various diseases, for example, the symptom of a pain, migraine and the disease of a central nervous system, for example, an uneasy condition, schizophrenia and depression, and a list.

[0036] Therefore, it is not in need of the attempt which develops a substance P antagonist. However, a series of substance P antagonists developed until now are peptide system compounds, and since it is unstable in metabolic turnover, they cannot be used as a remedy active substance. On the other hand, the useful salt is stable in metabolic turnover on the substance P antagonists of the formula I prepared according to this invention, and those

remedies, therefore it is dramatically suitable for the therapy treatment of said disease.

[0037] In the first place, this invention is R1. It is unsubstituted or sets for a phenyl component. By low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, phenyl - permuted by trifluoromethyl, It is a diphenyl -, naphthyl -, or fluorenyl-low-grade alkyl group and unsubstituted, or sets for a phenyl component. With a halogen And/or, the phenoxy-low-grade alkyl group permuted by thoria ZORIRU, The hetero aryl-low-grade alkyl group which has the aza--hetero aryl which is 6 members as a hetero aryl group, is a monocycle type, or is a 2 ring type, and consists of six membered-rings, 5, or 6 membered-rings, Are unsubstituted or by low-grade alkyl by low-grade ARUKOKISHI By G low-grade alkylamino with the hydroxyl with a halogen It is noil or the cycloalkyl carbonyl group of 3 - 8 member, and unsubstituted, or sets for a phenyl component. cyano \*\* -- and/or, the benzoyl permuted by trifluoromethyl, naphthoyl, and full -- me -- by low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, the phenyl - or diphenyl-low-grade alkanoyl radical permuted by trifluoromethyl, The hetero aryl-low-grade alkanoyl radical which has the aza--hetero aryl which is 6 members as a hetero aryl group, is a monocycle type, or is a 2 ring type or a 3 ring type, and consists of six membered-rings, one piece, or two 5 or 6 membered-rings, It is unsubstituted or sets for a phenyl component. By low-grade alkyl by low-grade ARUKOKISHI By G low-grade alkylamino, with a halogen, and/or, the phenyl-low-grade alkoxy carbonyl or N-phenylcarbamoyl radical permuted by trifluoromethyl, Or it is the acyl group of the alpha-amino acid which may be carried out N-permutation by carbamoyl-low-grade alkanoyl. or -- as a peptide configuration unit -- nature -- existing -- and low-grade alkanoyl -- R2 Whether it is cycloalkyl of 5 - 7 member, or it is unsubstituted by or the low-grade alkyl combined in aromatic series By low-grade ARUKOKISHI, with a halogen, and/or, the phenyl permuted by trifluoromethyl, It is the monocycle type aza--hetero aryl group of naphthyl or 6 members, and is R3. Hydrogen, Low-grade alkyl, carbamoyl, low-grade alkanoyl, and carboxy-low-grade alkanoyl or carboxy-low-grade ARUKE noil, Low-grade alkoxy carbonyl-low-grade alkyl, carbamoyl-low-grade alkanoyl, N-Monod or N, and N-G low-grade alkyl carbamoyl-low-grade alkanoyl, It is N-cycloalkyl carbamoyl-low-grade alkanoyl or N-phenylcarbamoyl-low-grade alkanoyl, and is R4. Are unsubstituted or by or low-grade alkyl low-grade ARUKOKISHI -- a halogen -- and/or, it being the phenyl permuted by trifluoromethyl, naphthyl, a pyridyl radical, or unsubstituted, or by low-grade alkyl And/or, C-permutation of is done by trifluoromethyl and N-permutation is carried out by the case by low-grade alkanoyl. low-grade ARUKOKISHI -- a halogen -- And it is the hetero aryl group which consists of Monod of 5 which may be hydrogenated selectively, or 6 members, G aza-- or an OKISA-hetero aryl group, and the aryl group of 6 members. X1 By methylene, ethylene, and low-grade alkanol, or the carbonyl group which may be ketal-ized by low-grade alkane diol, The hydroxy methylene group which may be etherified by low-grade alkanol, Or it is direct coupling and X2 is carbonyl,

low-grade alkylene, or direct coupling. And X3 Carbonyl, oxo--low-grade alkylene, oxo-(aza)-low-grade alkylene, Or about N atom, 1, 2, or in existing, it sets to the 3rd place. or -- or it is unsubstituted -- or phenyl -- by carboxyl low-grade alkoxy carbonyl -- carbamoyl -- N-Monod or N, and N-G low-grade alkyl carbamoyl -- or it is related with compound [ of the formula I which is the low-grade alkylene group permuted by hydroxymethyl ];, and those salts.

[0038] Especially this invention is R1. It is unsubstituted or sets for a phenyl component. By low-grade alkyl low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, phenyl - or diphenyl-C1-C4 permuted by trifluoromethyl alkyl -- For example, benzyl, 2, 4-dichloro benzyl, 3, 5-ditrifluoromethyl benzyl, or it is 2-phenylethyl or 2, and 2-diphenyl ethyl and unsubstituted -- or a phenyl component -- setting -- a halogen -- and/or, phenoxy-C1-C4 permuted by thoria ZORIRU alkyl -- Pyridyl - or kino RINIRU-C1-C4 Are alkyl, for example, 4-KINORI nil methyl, and unsubstituted, or by or low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, the benzoyl permuted by trifluoromethyl, For example, benzoyl, 3-low-grade alkyl -, 3-low-grade alkoxy -, 3-halogeno -, Are 3-dimethylamino -, 3, 5-JI low-grade alkyl -, 3, 5-JI low-grade alkoxy -, 3, and 5-dihalogeno - or 3, 5-ditrifluoromethyl-benzoyl, and unsubstituted, or by or low-grade alkyl low-grade ARUKOKISHI - G low-grade alkylamino -- a halogen -- and/or, it being the naphthoyl permuted by trifluoromethyl, for example, 1-, 2-naphthoyl, and unsubstituted, or by low-grade alkyl low-grade ARUKOKISHI -- a halogen -- and/or, it being the pyridyl carbonyl permuted by trifluoromethyl or KINORI nil carbonyl, and unsubstituted, or by low-grade alkyl With a halogen by G low-grade alkylamino with low-grade ARUKOKISHI And/or, the cycloalkyl carbonyl of 5 permuted by trifluoromethyl - 7 members, For example, cyclohexyl carbonyl, 3-methyl -, 3-methoxy -, 3-chloro -, 3-dimethylamino -, 3, 5-dimethyl -, 3, 5-dimethoxy -, It is 3 and 5-dichloro - or 3, 5-ditrifluoromethyl-cyclohexyl carbonyl, and unsubstituted, or sets for a phenyl component. By low-grade alkyl low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, phenyl - or diphenyl-C1-C4 permuted by trifluoromethyl alkanoyl -- It is 2 and 2-diphenyl acetyl or 2, 3-diphenyl propionyl, and unsubstituted, or sets for a phenyl component. For example, by low-grade alkyl low-grade ARUKOKISHI -- G low-grade alkylamino -- a halogen -- and/or, N-phenylcarbamoyl which may be permuted by trifluoromethyl or radical [ of Formula Ia ]: -- [Formula 17]



(Among a top type, R5 is hydrogen and unsubstituted or by the hydroxyl) By the phenyl in which a hydroxy permutation may be carried out by amino by mercapto carboxyl -- carbamoyl - - or C1-C4 permuted by ureido It is alkyl. R6 [ and ] C2-C7 it is alkanoyl -- it is -- or it is [ whether R2 is cycloalkyl of 5 - 7 member, or ] unsubstituted -- or C1-C4 By alkyl C1-C4 By ARUKOKISHI, with a halogen, and/or, phenyl permuted by trifluoromethyl, It is naphthyl or a

pyridyl radical and is R3. Hydrogen and C1-C7 Alkyl, Carbamoyl and C2-C7 Alkanoyl and carboxy-C1-C4 Alkanoyl or carboxy-C2-C4 It is ARUKE noil and is R4. It is unsubstituted or is C1-C4. By alkyl C1-C4 By ARUKOKISHI, with a halogen, and/or, phenyl or naphthyl permuted by trifluoromethyl, Or unsubstituted pyridyl, benzofuranyl one, the indolyl, 2, 3-dihydroindolyl, They are benzimidazolyl, quinolyl or 1, 2 and 3, and 4-tetrahydro kino RINIRU. X1 Methylene, hydroxy methylene, and C1-C4 Alkoxy methylene, Carbonyl and G C1-C4 They are alkoxy methylene or direct coupling. X2 C1-C7 They are alkylene, carbonyl, or direct coupling. And X3 Carbonyl and C1-C4 Alkylene and carboxy-C1-C4 Alkylene, C1-C4 Alkoxy carbonyl-C1-C4 Alkylene and carbamoyl-C1-C4 Alkylene or hydroxymethyl-C1-C4 It is related with compound [ of the formula I which is alkylene ];, and those salts.

[0039] this invention -- especially -- R1 or it is unsubstituted -- or C1-C4 alkyl -- for example, methyl -- C1-C4 ARUKOKISHI -- for example, methoxy -- a halogen -- and/or, the benzoyl, the naphthoyl, or phenyl-C1-C4 permuted by trifluoromethyl alkanoyl -- it is -- or unsubstituted pyridyl carbonyl or KINORI nil carbonyl -- it is -- or radical [ of Formula Ia ]: -- [Formula 18]



(Among a top type, R5 is hydrogen and unsubstituted or by the hydroxyl) By the phenyl in which a hydroxy permutation may be carried out by amino by mercapto carboxyl -- carbamoyl - - or C1-C4 permuted by ureido alkyl -- For example, methyl, isopropyl, isobutyl, the second butyl, hydroxymethyl, Mercaptomethyl, 2-methyl mercapto ethyl, 3-ureido propyl, 4-amino butyl, carboxymethyl, carbamoyl methyl, 2-carboxy ethyl, They are 2-carbamoyl ethyl, benzyl, or 4-hydroxybenzyl. And R6 C2-C7 Alkanoyl, for example, acetyl, a propionyl, they are the butyryl or pivaloyl -- it is -- R2 the cycloalkyl of 5 - 7 member -- It is cyclopentyl or cycloheptyl especially cyclohexyl or the second, is unsubstituted, or is C1-C4. By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy With a halogen, and/or, the phenyl permuted by trifluoromethyl, It is naphthyl or a pyridyl radical and is R3. Hydrogen and C1-C7 Alkyl, For example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, The second butyl or tertiary butyl, carbamoyl, and C2-C7 Alkanoyl, For example, acetyl, a propionyl, the butyryl or pivaloyl, and carboxy-C1-C4 Alkanoyl, For example, succinoyl, a GURUTA roil, horse mackerel POIRU, or carboxy-C3-C5 ARUKE noil, For example, it is MAREIRU, FUMAROIRU, or a tart roil, and is R4. It is unsubstituted or is C1-C4. By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy With a halogen, and/or, phenyl or naphthyl permuted by trifluoromethyl, Or it is pyridyl, benzofuranyl one, the indolyl, unsubstituted benzimidazolyl, or unsubstituted quinolyl. X1 Methylene, hydroxy methylene, and C1-C4 Alkoxy methylene, For example, methoxy methylene, ethoxy methylene, propyloxy methylene, or butyloxy methylene, Carbonyl and G C1-C4 Alkoxy methylene, for example, dimethoxy methylene, Diethoxy methylene, dipropyl oxy-methylene, or dibutyl oxy-methylene, Or it is direct coupling and is X2.

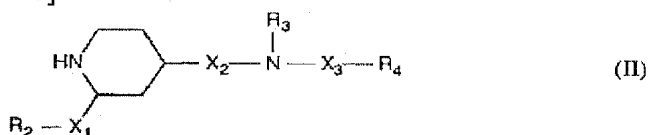
To C1-C7 alkylene, for example, methylene, or the second, ethylene or 1, 3-propylene, It is carbonyl or direct coupling and is X3. Carbonyl and C1-C4 Alkylene, For example, methylene, ethylene or 1, 3-propylene, and carboxy-C1-C4 Alkylene, For example, 1, 3-(2-carboxy) propylene, 1, and 4-(2-carboxy) butylene or 1, 4-(3-carboxy) butylene, C1-C4 Alkoxy carbonyl-C1-C4 Alkylene, For example, 1, 3-(2-C1-C4 alkoxy carbonyl) propylene, 1, 4-(2-C1-C4 alkoxy carbonyl) butylene, 1, 4-(3-C1-C4 alkoxy carbonyl) butylene, 1, 5-(2-C1-C4 alkoxy carbonyl) pentene, 1 and 5-(3-C1-C4 alkoxy carbonyl) pentene or 1, 5-(4-C1-C4 alkoxy carbonyl) pentene (it is C1-C4 of each \*\*\*\* here alkoxy carbonyl) For example, mean methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, or butoxycarbonyl. Carbamoyl-C1-C4 Alkylene, 1 [ for example, ], 3-(2-carbamoyl) propylene, 1, 4-(2-carbamoyl) butylene, 1, 4-(3-carbamoyl) butylene, 1, 5-(2-carbamoyl) pentene, 1, and 5-(3-carbamoyl) pentene or 1, 5-(4-carbamoyl) pentene, Or hydroxymethyl-C1-C4 Alkylene, 1 [ for example, ], 3-(2-hydroxymethyl) propylene, 1, 4-(2-hydroxymethyl) butylene, 1, 4-(3-hydroxymethyl) butylene, It is related with compound [ of the formula I which is 1 5-(2-hydroxymethyl) pentene, 1, and 5-(3-hydroxymethyl) pentene or 1, and 5-(4-hydroxymethyl) pentene ],, and its salt.

[0040] This invention is R1 preferably. It is unsubstituted or is C1-C4. By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy the atomic number -- 35 or less halogen -- for example, chlorine -- and/or, trifluoromethyl -- a single permutation or the benzoyl carried out 2 \*\*\*\*s -- Or unsubstituted naphthoyl or unsubstituted phenyl-C1-C4 It is alkanoyl and is R2. It is unsubstituted or is C1-C4. By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy the atomic number -- 35 or less halogen -- for example, chlorine -- and/or, trifluoromethyl -- a single permutation or the phenyl carried out 2 \*\*\*\*s -- Or it is unsubstituted pyridyl and is R3. Hydrogen, C1-C4 alkyl, For example, methyl, ethyl, propyl or isopropyl, carbamoyl, or C2-C7 Alkanoyl, For example, it is acetyl, a propionyl, the butyryl, or pivaloyl, and is R4. It is unsubstituted or is C1-C4. By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy the halogen of the following [ atomic number / 35 ] -- for example, chlorine -- and/or, trifluoromethyl -- a single permutation or the phenyl carried out 2 \*\*\*\*s -- Or unsubstituted naphthyl, pyridyl, benzofuranyl one, indolyl, It is benzimidazolyl or quinolyl and is X1. Methylene, hydroxy methylene, It is carbonyl or direct coupling and is X2. It is direct coupling and is X3. C1-C4 It is related with compound [ of the formula I which is ethylene or 1, and 3-propylene ],, and its salt alkylene, for example, methylene, or the second.

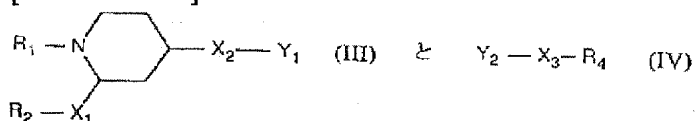
[0041] This invention is R1 especially. It is unsubstituted or is C1-C4. By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy the atomic number -- 35 or less halogen -- for example, chlorine -- and/or, trifluoromethyl -- a single permutation or the benzoyl carried out 2 \*\*\*\*s -- Or it is unsubstituted naphthoyl and is R2. Are phenyl or the atomic number with 35 or less halogen And/or, they are a single permutation or the phenyl carried out

2 \*\*\*\*s by trifluoromethyl. for example, chlorine -- R3 It is hydrogen and is R4. It is unsubstituted kino RINIRU and is X1. It is methylene. X2 It is direct coupling and is X3. C1-C4 It is related with compound [ of the formula I which is ethylene or 1, and 3-propylene ],, and its salt alkylene, for example, methylene, or the second. Especially this invention relates to the compound of the formula I specified in an example, and its salt.

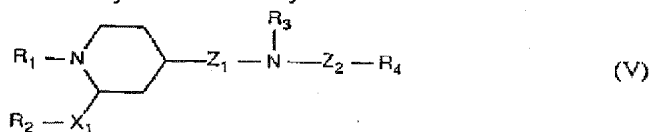
[0042] This invention relates to the preparation approach of the compound of this invention based on the approach of further itself known. this approach -- a-type II compound: -- [Formula 19]



(R2, R3, R4, X1, X2, and X3 have above semantics among a top type) It is a radical R1 to inside. It introduces or is [0043]. b) Formula III A compound and the compound of Formula IV: [Formula 20]



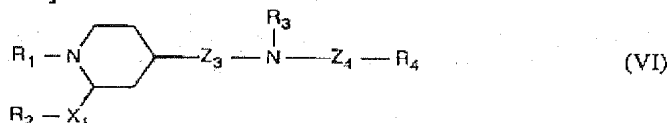
the inside of a top type, and Y1 -- the radical of formula-N(R3)-H -- it is -- Y2 [ and ] -- the hydroxyl -- The reactant esterification hydroxyl or X3 When it is carbonyl, It is the etherified hydroxyl or is Y1. Hydroxyl, The reactant esterification hydroxyl or X2 When it is carbonyl, It is the etherified hydroxyl and is Y2. It is the radical of formula-N(R3)-H and is R2, R3, R4, X1, and X2. And X3 Or it has above semantics, those salts are made to condense together or it is [0044]. c) radical X2 X3 one side -- alkylene -- it is -- another side -- alkylene, carbonyl, or X2 it is -- a case -- direct coupling or X3 a case -- hydroxymethyl -- or -- in order to be preparation of the compound of the formula I which is the alkylene group which may be permuted by the carboxyl which may be esterified or amidated -- compound [ of Formula V ]: -- [Formula 21]



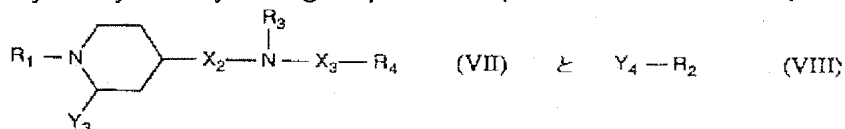
Or it is the alkylene group permuted by the hydroxyl. the inside of [ top type, and Z1 -- radical-N(R3)- receiving -- an alpha position -- setting -- oxo-\*\* -- Z2 [ and ] Or it is the alkylene group which may be permuted by the carboxyl which may be esterified or amidated. alkylene, carbonyl, or hydroxymethyl -- Z1 [ or ] alkylene, carbonyl, or direct coupling -- it is -- Z2 [ and ] Or it is the alkylene group permuted by the hydroxyl. radical-N(R3)- receiving -- an alpha position -- setting -- oxo-\*\* -- And R2, R3, R4 and X1, and X2 And the compound of whether in]



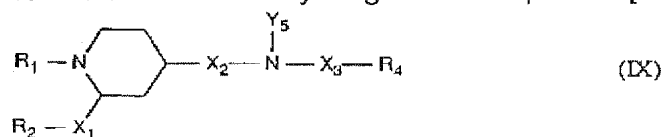
which has the semantics of the above [ X3 ], or its salt, oxo-\*\*\*\* of an alpha position transposes hydroxyl to hydrogen by reduction to radical-N(R3)-, and Formula VI: It is [Formula 22].



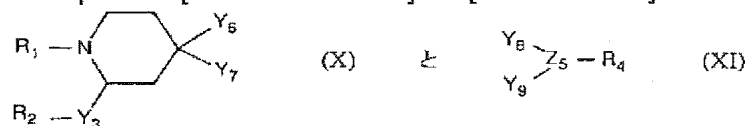
The inside of [ top type and Z3 are the radicals of formula-C(Ra) =C(Rb)-. Z4 Alkylene, Or it is the alkylene group which may be permuted by the carboxyl which may be esterified or amidated. carbonyl or hydroxymethyl -- Or Z3 It is alkylene, carbonyl, or direct coupling, and is Z4. It is the radical of formula-C(Ra) =C(Rb)- and is Ra here. And Rb In] which is hydrogen or low-grade alkyl respectively The radical of formula-C(Ra) =C(Rb)- is returned to radical-CH (Ra)-CH(Rb)- which corresponds by reduction of a double bond, or it is [0045]. d) X1 It is Formula VII in order to be preparation of the compound of the formula I which is carbonyl or a hydroxy methylene group. A compound and the compound of Formula VIII: [Formula 23]



(-- or [ that one of the inside of a top type and the radicals Y3 and Y4 is the formyl ] -- or it is the carboxyl group by which have been esterified [ anhydride-ization or ], another side is a metallicity radical, and R2, R3, R4, X2, and X3 have above semantics --) -- together -- condensing -- making -- [0046] [ or ] e) R3 in order to be preparation of the compound of the formula I which is hydrogen -- compound [ Of Formula IX ]: -- [Formula 24]



(Among a top type, Y5 is an amino protective group, and R2, R4, X1, X2, and X3 have above semantics) or the salt to radical Y5 it \*\*\*\*s -- making -- fX3 [ or ] in order to be preparation of the compound of the formula I which is alkylene -- the compound Of Formula X, and compound [ of Formula XI ]: -- [Formula 25]



Y6 is the radical of formula-N(R3)-H among [ top type, and Y7 is hydrogen. Y8 Y9 It becomes together and is those with oxo-\*\*, and Z5. X3 [ whether it is a corresponding ARUKA nil ylidene radical and ] Y6 [ or ] Y7 together -- becoming -- those with oxo-\*\*, and Y8 the radical of

formula-N(R3)-H -- it is -- Y9 hydrogen -- it is -- Z5 [ and ] Radical X3 [it is -- ] is condensed together under reduction conditions -- making -- 0047] And it is characterized by to change the salt which can change into a salt the isolation compound which can be obtained according to/or this approach by changing the obtained compound into the compound of another formula I, and classifying the mixture of the isomer which can be obtained according to this approach for the component, and separating a desirable isomer in each \*\*\*\*, or can obtain according to this approach if it is a request into a corresponding isolation compound.

[0048] Preparation of new starting material and intermediate field is performed in the implementation of a reaction according to this approach, and a list respectively like the reaction of known starting material and intermediate field, and the formation approach. If suitable for a reaction condition, for example, temperature, and a flow and pressure requirement, and a list in the adjuvant used for each \*\*\*\* here, for example, a catalyst, a condensing agent and a solvolysis agent and/or a solvent or a diluent, and a list, unless protection gas is mentioned specially henceforth, it is a thing in ordinary use.

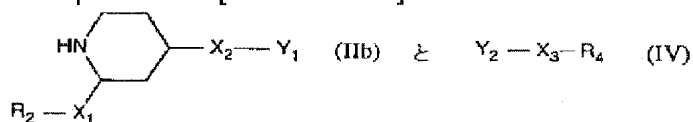
[0049] Radical R1 according to the strange method a Installation is a radical R1 by the conventional method. Matter to introduce, for example, a reaction (the aroyl by which R1 may be permuted here --) with the acylating agent of formula R1-Ya (IIa1) Hetero aroyl, cycloalkyl carbonyl, aryl alkanoyl, Or it is the acyl group of the alpha-amino acid which may be formed into N-alkanoyl. or [ that they are hetero aryl alkanoyl or an aryl carbamoyl group ] -- And Ya Hydroxy \*\*, for example, hydroxy \*\*, which may be etherified phenyloxy carbonyl [ which has permuted / low-grade alkoxy carbonyl or ] or reactant esterification hydroxy \*\*, for example, halogen, especially chlorine, or formula-O-R1 a radical -- it is -- or a reaction (the aralkyl by which R1 may be permuted here --) with aralkyl-izing of formula R1-Yb (IIa2), aryloxy alkylation, or a heteroarylalkyl-ized agent It is aryloxy alkyl or a hetero aralkyl radical, and is Yb. Reactant esterification hydroxyl, For example, a halogen, for example, chlorine, a bromine, iodine, or a sulfonyloxy radical, for example, a benzene sulfonyloxy radical which has permuted [ the alkane sulfonyloxy radical or ], for example, methane -, ethane -, benzene -, p-toluene -, or p-bromobenzene-sulfonyloxy radical -- it is -- Or it is performed by the reaction (R1 is the aralkyl, the aryloxy alkyl, or the hetero aryl group which may be permuted here) with formula R1=O (IIa3) under reduction conditions.

[0050] If required, an activity will be done under existence of the pyrolysis of the ammonium salt formed as intermediate field, a condensing agent, for example, a water binder, or a basic condensing agent, and existence of a solvent or a diluent. The reaction with the acid of a formula IIa1 (Y=COOH) Preferably under existence of water binder, for example, N, and N-dicyclohexylcarbodiimide It is performed by the pyrolysis of the ammonium salt formed first. On the other hand, or a reaction with the anhydride of a formula IIa1 (Y= halogen or -O-(C=O)-R1), and the reaction with a formula IIa2 Preferably A basic condensing agent, for example, an

alkali-metal hydroxide, or a carbonate, Or it is carried out under existence of the second class organic amine with the third class or steric hindrance, for example, Tri low-grade alkylamine, for example, triethylamine, diisopropylamine, or an aromatic series nitrogen base, for example, a pyridine.

[0051] The reaction of the compound of a formula IIa3 is hydrogen and a hydrogenation catalyst, for example, platinum, a palladium catalyst, or Raney. It is carried out under a reaction condition in the solvent which is inactive in low-grade alkanol, for example, a methanol, ethanol, JI low-grade alkyl or the low-grade alkylene ether, for example, diethylether, dioxane, or a tetrahydrofuran preferably under existence of nickel or existence of a 2 light-metal hydride, for example, a sodium borohydride, or hydrogenation cyano boron sodium.

[0052] the starting material of Formula II -- a conventional method -- for example, bottom-type compound: -- [Formula 26]



By making it react mutually, about the strange method b, it is mentioned later, and can make and prepare.

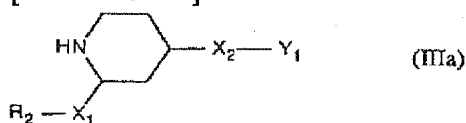
[0053] formula III given in the strange method b or the reactant esterification hydroxyl in the starting material of IV -- a halogen, for example, chlorine, a bromine, an iodine atom, or X3 the case where it is not carbonyl -- a sulfonyloxy radical, for example, methane sulfonyloxy, a p-toluenesulfonyloxy radical, or X3 the case where it is carbonyl -- formula -O-(C=O)-R4 A radical is meant. [ for example, ] The etherified hydroxyl means the phenyloxy which has permuted [ low-grade alkoxy \*\*, for example, methoxy, or ethoxy \*\* or ]. The anhydride-ized hydroxyl is a halogen especially chlorine, or a formula. -O-(C=O)-R4 It is a radical.

[0054] Formula III The reaction of a compound and the compound of Formula IV is performed according to a conventional method under existence of the pyrolysis of the ammonium salt formed as intermediate field, a condensing agent, for example, a water binder, or a basic condensing agent, and existence of a solvent or a diluent. Formulas IV or III The reaction with an acid (Y2 or Y1 =OH) Preferably under existence of water binder, for example, N, and N-dicyclohexylcarbodiimide Or it is performed by the pyrolysis of the ammonium salt formed first. On the other hand, they are Formula IV or III. A reaction with reactant ester (Y2 or Y1 = reactivity esterification hydroxyl), Formula IV, or III The reaction with an acid anhydride (Y2 or hydroxyl formed into the Y1 = anhydride) Preferably A basic condensing agent, for example, an alkali-metal hydroxide, or a carbonate, Or it is carried out under existence of the second class organic amine with the third class or steric hindrance, for example, Tri low-grade alkylamine, for example, triethylamine, diisopropylamine, or an aromatic series nitrogen base,

for example, a pyridine.

[0055] formula III starting material was mentioned above under the strange method a according to the conventional method -- as -- for example, compound [ of Formula IIIa ]: --

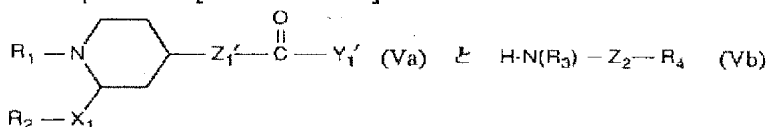
[Formula 27]



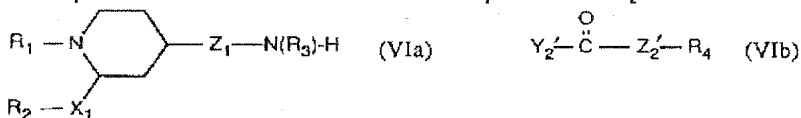
It is a radical R1 to inside. It can prepare by introducing.

[0056] Oxo-\*\*\*\*\* of an alpha position reduction of the double bond of the radical of the reduction permutation by the hydrogen of hydroxyl, or formula-C(Ra)=C(Rb)- to radical-N(R3)- according to the strange method c the [ for example, / of contact hydrogenation, i.e. a hydrogenation catalyst, for example, the periodic table ] -- VIIIb A group's metal or metallic compounds, for example, platinum, oxidization platinum, palladium/carbon, or Raney By hydrogen processing under existence of nickel Or it is performed by the reaction of a 2 light-metal hydride, for example, boron hydride alkali metal, for example, hydrogenation cyano boron sodium, or processing with a formic acid.

[0057] The starting material of Formulas V or VI is Formula Va. A compound and formula Vb Compound: [Formula 28]



(-- a top -- a formula -- inside -- Z -- one -- ' -- direct coupling -- it is -- or -- or -- one -- C -- an atom -- compaction -- carrying out -- having had -- a radical -- X -- two -- it is -- Y -- one -- ' -- hydrogen -- low-grade -- alkyl -- or -- isolation -- etherifying -- having had -- or -- reactivity -- esterification -- carrying out -- having had -- the hydroxyl -- it is -- and -- Z -- two -- having mentioned above -- semantics -- having --) -- condensation -- or -- a formula -- VIa A compound and formula VIb compound: -- [Formula 29]

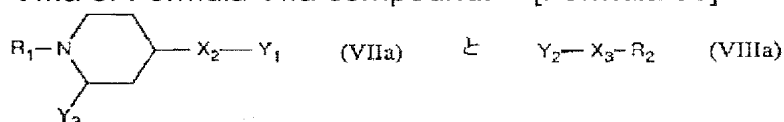


(-- a top -- a formula -- inside -- Z -- one -- the above -- semantics -- having -- Z -- two -- ' -- direct coupling -- it is -- or -- or -- one -- C -- an atom -- compaction -- carrying out -- having had -- a radical -- X -- three -- it is -- Y -- two -- ' -- hydrogen -- low-grade -- alkyl -- or -- isolation -- etherifying -- having had -- or -- reactivity -- esterification -- carrying out -- having had -- the hydroxyl -- it is --) -- condensation -- it can prepare . Formula Va Y1 ' or Formula VIb in a compound When Y2 ' in a compound is hydrogen or low-grade alkyl, the response compound

of Formula V is especially formed in basicity or a neutral medium under a mild reaction condition, and the response compound of Formula VI is formed especially in an acid medium under a severe reaction condition. As for this, in the below-mentioned case, subsequently, the response compound of Formula VI is formed of desorption of water from the compound of Formula V with formation of the response compound of Formula V as intermediate field. The starting material of Formulas V and VI can be parallel, and can also be manufactured. It is Formula Va under [ of said reducing agents ] one existence, without forming the intermediate field of Formulas V or VI on that spot, and isolating in the desirable mode of this invention. Vb Or formula VIa VIb By performing condensation of starting material, it is returned to the response compound of Formula I.

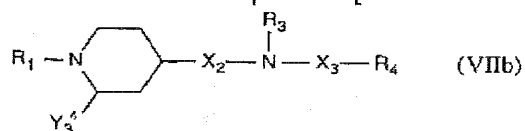
[0058] each of the strange method d -- formula VII Or carboxyl Y3 by which have been esterified [ anhydride-ization in the starting material compound of VIII, or ] Or Y4 For example, halogeno carbonyl or Y4 A case is formula  $R_2-C(=O)-O-$  - Radical, And metallicity radical Y3 Or Y4, for example, a formula, - MII/2 or MII-Hal (MII is the metal atom of the IIB group of the periodic table of an element, for example, Mg or Zn, here) is meant. Formula VII And the reaction of the compound of VIII is performed according to a conventional method in an ether system solvent, for example, aliphatic series, or alicyclic ether, for example, diethylether, methoxy butane, dibutyl ether, a tetrahydrofuran, or dioxane.

[0059] Y3 or [ that it is the formyl ] -- or formula VII which is the carboxyl by which have been esterified [ anhydride-ization or ] starting material -- for example, the compound and Formula VIIIa of Formula VIIa compound: -- [Formula 30]



Y1 is the radical of formula-N(R3)-H among [ top type. Y2 The hydroxyl or the hydroxyl by which reactant esterification was carried out, Or X3 When it is carbonyl, they are etherification or the anhydride-ized hydroxyl. Or Y1 Hydroxyl or hydroxyl by which reactant esterification was carried out, Or X2 When it is carbonyl, they are etherification or the anhydride-ized hydroxyl. And Y2 It is the radical of formula-N(R3)-H and is R2, R3, R4, X1, and X2 here. And X3 By making] which has above semantics, or its salt condense together, as indicated under for example, the strange method b, it can prepare.

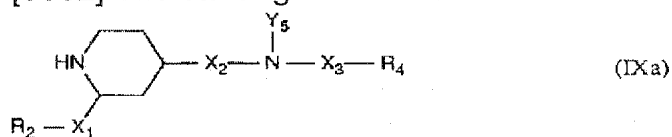
[0060] Y3 Or Y4 Formula VII which is a metallicity radical and the starting material of VIII -- desirable -- compound [ of Formula VIIb ]: -- [Formula 31]



making it react with the metal of Formula MII (inside of top type and Y3 ' is a halogen atom especially chlorine, a bromine, or iodine) -- the compound (here -- Y4 ' -- hydrogen or a halogen atom --) of; type Y4 '-R2 (VIIIb) Formula VIIIb whose; Y4 ' is hydrogen by leaving that it is especially chlorine, a bromine, or iodine A compound Organometallic compound, For example, formula VIIIb; or whose Y4 ' is a halogen atom by making it react with the metal derivative of aliphatic hydrocarbon, for example, butyl lithium, It is prepared by making a compound react with the metal of Formula MII.

[0061] Amino protective group Y5 in the starting material of the formula IX given in the strange method e For example, they are the low-grade alkanoyl radical which may be halogenated, for example, trifluoro acetyl, and the acyl group guided from the monoester of carbonic acid, for example, low-grade alkoxy carbonyl, an alpha-phenyl-low-grade alkoxy carbonyl group, for example, the third butyloxy carbonyl, benzyloxycarbonyl, or a silyl radical, for example, a Tori low-grade alkyl silyl radical, for example, a trimethylsilyl radical. Desorption of an amino protective group follows a conventional method, for example, is acid treatment or Y5. The compound IX which is halogenation low-grade alkanoyl, for example, trifluoro acetyl, is left, and it is preferably carried out by processing for example, with a 2 light-metal hydride, for example, a sodium borohydride, in low-grade alkanol, for example, a methanol, by reduction desorption.

[0062] The starting material of Formula IX is Formula IXa. Response compound: [Formula 32]



since -- it can leave and can prepare like the strange method a.

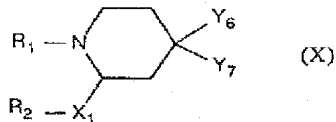
[0063] the reaction of the compound of the formula X according to the strange method f, and the compound of Formula XI -- for example, desorption of water -- for example, -- especially -- azeotropic distillation with toluene -- subsequently it is performed by reduction with borane, a 2 light-metal hydride, for example, boron hydride alkali metal, for example, sodium borane, or hydrogenation cyano boron sodium. R1 The acyl group defined in Formula I is expressed, and it is X1. It is hydroxy methylene and is Y6. Y7 The starting material of Formula X which becomes together and expresses OKISO, and those salts permitted on a remedy show the same pharmacology property as an end product and the equivalent activity of Formula I.

[0064] Andrews And it sets to Helme, Regul.Pept.25, and the model based on the laboratory procedure of 267-275 (1989). The following ED50 value was acquired. : ( ) [ 2R\* , ] [ 1'R\* ] -1- 3 -- 5 - screw trifluoromethyl benzoyl-2-[1'-hydroxy-1'-(4-chlorophenyl) methyl]-4-piperidone (example 85): -- 5.5 mg/kg iv; (2R\* --) 1'S\*-1-(3, 5-dimethylbenzoyl)-2-[1'-hydroxy-1'-(3, 4-dichlorophenyl) methyl]-4-piperidone (example 90b): 2.0 mg/kg iv.

[0065] Furthermore, Lundberg et al., Proc.Nat.Acad.Sci.(USA) 80, and 1120-1124 In the model

based on a laboratory procedure The following ED50 value was acquired. : ( ) [ 2R\*, ] [ 1'R\* ] - 1- 3 -- 5 - screw trifluoromethyl benzoyl-2-[1'-hydroxy-1'-(4-chlorophenyl) methyl]-4-piperidone (example 85): -- 9.0 mg/kg iv; (2R\* --) 1'S\*-1-(3, 5-dimethylbenzoyl)-2-[1'-hydroxy-1'-(3, 4-dichlorophenyl) methyl]-4-piperidone (example 90b): 6.5 mg/kg iv.

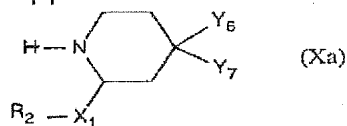
[0066] therefore, this invention -- 1-acyl piperidone [ of Formula X ]: -- [Formula 33]



the aroyl by which R1 may be permuted among a top type, and hetero aroyl -- Cycloalkyl carbonyl, aryl alkanoyl, hetero aryl alkanoyl, They are aryl alkoxy carbonyl or an aryl carbamoyl group. Or it is the acyl group of the alpha-amino acid which may be carried out N-permutation by carbamoyl-low-grade alkanoyl. or low-grade alkanoyl -- R2 It is the aryl or the hetero aryl group which has permuted [ cycloalkyl or ]. X1 Hydroxy methylene is expressed and it is Y6. Y7 And it becomes together and expresses OKISO, it is related with those utilization as a remedy active substance at the drugs and the list containing the preparation approaches of the compound of those salts and this invention, and those compounds. It sets to those compounds and is R2. It has the semantics preferably pointed out about the compound of Formula I, and the semantics pointed out especially about the compound of the desirable formula I especially.

[0067] This invention is R1 most preferably. Benzoyl and C1-C4 By alkyl For example, by methyl, it is C1-C4. By ARUKOKISHI, by for example, methoxy the atomic number -- 35 or less halogen -- for example, chloro -- and/or, trifluoromethyl -- a single permutation or the benzoyl carried out 2 \*\*\*\*s -- Or unsubstituted naphthoyl is expressed and it is R2. Phenyl or the atomic number with 35 or less halogen for example, chloro -- and/or, trifluoromethyl -- a single permutation or the phenyl carried out 2 \*\*\*\*s -- expressing -- Y6 [ and ] Y7 It is related with the compounds of Formula X which become together and express OKISO, and those salts. Especially this invention relates to the compounds and those salts of Formula X given in an example.

[0068] R1 And R2 It has the semantics of indication and is X1. Hydroxy methylene is expressed and it is Y6. Y7 The compounds of Formula X which become together and express OKISO, and those salts are prepared by the approach of itself known. Those manufacture approaches are Formulas Xa. Compound: [Formula 34]



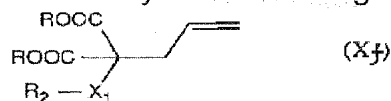
Radical R1 Make it condense with \*\* suitable for introducing, and if it is a request Change the

obtained compound into the compound of another formula I, and the mixture of the isomer which can be obtained according to this approach is classified for the component. And it is characterized by changing into a corresponding isolation compound the salt which can change into a salt the isolation compound which can be obtained according to/or this approach by separating a desirable isomer in each \*\*\*\*, or can be obtained according to this approach.

[0069] Radical R1 \*\* suitable for introducing is formula R1-Y10. It is the compound of (Xb). Y10 here The reactant esterification hydroxyl, for example, a halogen, or a sulfonyloxy radical, For example, benzene -, p-toluene -, or methane sulfonyloxy is expressed. Or R1 Aroyl -, hetero aroyl -, cycloalkyl carbonyl -, Aryl alkanoyl -, hetero aryl alkanoyl -, aryl alkoxy carbonyl -, or an aryl carbamoyl group, By low-grade alkanoyl, or when [ or ] the acyl component of the alpha-amino acid whose N-permutation may be done by carbamoyl-low-grade alkanoyl is expressed, hydroxy \*\*, for example, the halogen, by which Y10 was etherified -- and/or, low-grade alkoxy \*\*\*\* which may be permuted with nitroglycerine is phenyloxy.

[0070] Said condensation is performed by for example, a methylene chloride/underwater one in a water content two phase system under existence of for example, a basic condensation assistant preferably under existence of for example, an alkali-metal hydrogencarbonate, for example, a sodium hydrogencarbonate. The compound of Formula Xa N-protection piperidine-4-on-ketal, for example, 1-(tert-butyloxy carbonyl) piperidine-4-on-ethylene ketal for example, a hydrocarbon metal, for example, a hydrocarbon alkali-metal derivative, -- preferably under existence of a low-grade alkyl lithium compound, for example, sec-butyl lithium Preferably, it sets for example, in diethylether in an ether system solvent at -30 degrees C - -80 degrees C, for example, -60 degrees C - -75 degrees C, and is formula R2-CH=O. It can obtain by making it react with the aldehyde of (Xc).

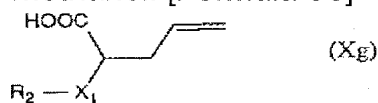
[0071] Y6 Table *Perilla frutescens* (L.) Britton var. *crispa* (Thunb.) Decne. of the radical of formula-N(R3)-H is carried out, and it is Y7. The compound showing hydrogen of Formula X for example, -- desirable -- the compound (here -- Y -- the reactant esterification hydroxyl --) of formula R2-X1-Y (Xd) for example, the benzene sulfonyloxy which has permuted [ a halogen low-grade alkane sulfonyloxy, or ] -- it is -- under existence of alkali-metal low-grade ARUKANORATO, for example, sodium methano RATO In low-grade alkanol, for example, a methanol, or under existence of sow DAMIDO in toluene it condenses with the low-grade alkyl swine-2-en -1 of formula CH<sub>2</sub>=CH-CH<sub>2</sub>-CH (COOR)<sub>2</sub> (Xe; R= low-grade alkyl), and a 1-dicarboxy rate -- making -- resultant [ of Formula Xf ]: -- [Formula 35]



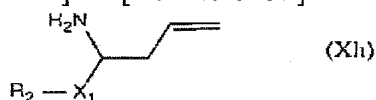
The acid of the formula Xg obtained by hydrolyzing and carrying out a decarboxylation by processing with an alkali-metal hydroxide, for example, a potassium hydroxide, in an aquosity



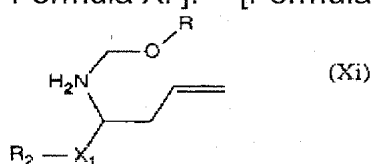
methanol: [Formula 36]



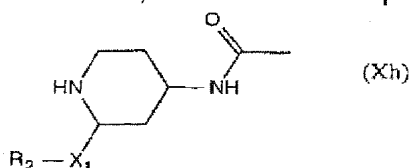
for example, after processing by the halogenating agent, for example, an oxalyl chloride, or the thionyl chloride -- a reaction with ammonia -- amidating -- and response amine [ of Formula Xh ]: -- [Formula 37]



after it is alike, and making it decompose, for example, protecting the amino group according to acylation, this is condensed with the halogenation low-grade alkoxy methyl of formula RO-CH2-Hal (Xf; R= low-grade alkyl; Hal = halogen), for example, chloro wood ether, under existence of a sodium hydroxide in dichloromethane/underwater one -- making -- resultant [ of Formula Xi ]: -- [Formula 38]



acid treatment -- for example, Lewis acid, for example, a tin tetrachloride, and an iron(III) chloride processing by a titanium tetrachloride or proton acid, for example, a sulfuric acid, the chlorosulfonic acid, p-toluenesulfonic acid, the trifluoromethyl acetic acid, or methansulfonic acid -- N-protection compound [ of the inside of an acetonitrile and the formula Xj which corresponds in an acetic anhydride and other solvents, for example, dichloromethane, benzene, or toluene if required ]: -- [Formula 39]



Carry out \*\*\*\* condensation, an amino protective group is made to \*\*\*\*, racemic modification generated when required is classified to an enantiomer, and a conventional method is followed, for example, it is X1. As it mentioned above about manufacture of the compound showing hydroxy methylene of Formula X, it is a radical R1. It introduces and an amino protective group is prepared by acid treatment by making it \*\*\*\* by processing for example, with 6-N hydrochloric acid.

[0072] The compound which can be obtained according to this approach is convertible for the

compound of another formula I with a conventional method. For example, X1 As the compound of the formula I which is carbonyl is the basis of for example, the approach c or indicated preparation of the intermediate product of Formulas V and VI with the conventional method, it is X1. It can return to the response compound of the formula I which is hydroxy methylene. X1 is hydroxy methylene or it is X2. And/or, X3 It is it like the generation compound of the formula I which is carbonyl X1 and X2 And/or, X3 It is also possible to return to the response compound of the formula I which is methylene.

[0073] X1 The carbonyl group in the generation compound of the formula I which is the carbonyl formed into \*\* ketal can be made to separate by acid treatment according to a conventional method. On the contrary, carbonyl X1 It can ketal-ize by the reaction with suitable alcohol, for example, low-grade alkanol, or low-grade alkane diol.

[0074] Furthermore, R3 It is also possible to introduce the alkanoyl or ARUKE noil which may be permuted by carbamoyl and acylation in ordinary use by radicals R3 other than hydrogen, for example, alkylation in ordinary use, as indication of alkyl by condensation with isocyanic acid or halogenation carbamoyl in the generation compound of the formula I which is hydrogen. On the contrary, R3 An alkyl group can be made to \*\*\*\* by processing with the ester of a HAROGI acid, for example, methyl ester, in the generation compound of the formula I which are alkyl, especially methyl.

[0075] Furthermore, alkanoyl or ARUKE noil R3 in the generation compound of Formula I Or alkylene X3 The carboxyl esterified or amidated as a substituent can be hydrolyzed to carboxyl, or the carboxyl of isolation can be esterified or amidated conversely.

[0076] The generated salt is convertible for an isolation compound with processing with other salt plasticity acids which made reference by the approach of itself known in processing with a base, for example, an alkali-metal hydroxide, a metal carbonate, a hydrogencarbonate, or ammonia, the processing by other salt plasticity bases which made reference in induction, an acid, for example, an inorganic acid, for example, a hydrochloric acid, or induction.

[0077] In a suitable solvent which the mineral salt to form is insolubility, therefore is separated from a reaction mixture by the approach of itself known, for example, the generated salt can be changed into another acid addition salt by processing with the suitable metal salt, for example, the sodium, barium, or silver salt of another acid, and can be changed into a base salt by isolation of a free acid, and re-salt formation. The compound of the formula I containing a salt can also contain the solvent which could also obtain in the form of a hydrate or was used for crystallization.

[0078] In a suitable case, with the close relation between the new molecular entity of an isolation form, and the compound of the form of those salts, the above, the following isolation compounds, and those salts also mean the salt or isolation compound which corresponds, respectively on semantics and the object. The mixture of the generated diastereomer and the

mixture of racemic modification can be classified to a respectively pure diastereomer or respectively pure racemic modification a chromatography and/or fractional crystallization by the known approach based on a physicochemical difference of a component.

[0079] Optically obtained racemic modification by the known approach, for example with recrystallization from an activity solvent The acidity included in the compound of for example, the activity of a microorganism, or the formula I, Basicity or functionally The suitable optical-activity auxiliary compound for the radical which can be embellished, An optical-activity acid, a base, or optical-activity alcohol is used. The mixture of a diastereomer or racemic modification For example, the mixture or the functional derivative of diastereomeric salt, For example, it is separable into optical antipode by changing into the mixture of ester by dividing them into a diastereomer and making it an enantiomer required for each \*\*\*\* isolated from there according to a conventional method. The example of a suitable base, an acid, and alcohol An optical-activity alkaloid base, For example, strychnine, cinchonine, brucine, or D- or L-(1-phenyl) ethylamine, 3-PIPEKORIN, ephedrine, an amphetamine, and the same base obtained by composition, Optical-activity carboxylic-acid, sulfonic-acid, for example, quinic acid, or D- or L-tartaric acid, They are D- or L-G o-toluyl tartaric-acid and D- or L-malic acid, and D-, L-mandelic acid, or D-, L-camphor sulfonic acid, optical-activity alcohol, for example, a borneol, L-, or D-(1-phenyl) ethanol.

[0080] This invention relates also to the mode of an approach which the compound obtained as intermediate field in one phase of the above-mentioned approaches is left, and the remaining phase is carried out, or starting material is used in the form of a salt, or is formed especially under a reaction condition. This invention relates also to those utilization as selections, those preparation approaches, and intermediate field of the new starting material developed specially because of preparation of the compound concerning this invention, especially the starting material which brings about the compound of Formula I characterized as a desirable thing in induction.

[0081] The new molecular entity of Formula I can be used in the form of drugs. With the active substance of a therapy-effective dose, if these drugs are suitable, they contain a useful excipient on the remedy of the suitable inorganic or organic solid-state for the inside of intestines, for example, taking orally or parenteral administration, or a liquid. For example, the tablet or gelatine capsule containing a diluent, for example, a lactose, grape sugar, cane sugar, a mannitol, a sorbitol, a cellulose and/or lubricant, for example, diatomaceous earth, talc, stearin acid, its salt, for example, magnesium stearate, or calcium, and/or a polyethylene glycol is used. Further, if a tablet is a request, it can contain disintegrator, for example, starch, an agar, an alginic acid or its salt, for example, sodium alginate, and/or fizz mixture and also an absorbent, a coloring agent, flavors, and sweeteners in the starch of a binder, for example, magnesium aluminium silicate, starch, for example, corn, wheat, rice, or a potato, gelatin,

tragacanth, methyl cellulose, carboxymethylcellulose sodium and/or a polyvinyl pyrrolidone, and a list. Furthermore, it is also possible to use the new molecular entity of Formula I in the form of the pharmaceutical preparation in which parenteral administration is possible, or drop-by-drop-titration infusion. In the case of the freeze-drying article which is the aqueous solution or suspension of an isotonicity preferably, is independent, or contains an active substance with an excipient, for example, a mannitol, the solution of this form can be prepared before using them. Drugs can be sterilized and can contain the salt and/or buffer for adjusting/or an adjuvant, for example, a preservative, a stabilizer, a wetting agent, an emulsifier, a solubilizing agent, and osmotic pressure. If required, other pharmacological activity matter can be included further, these drugs are manufactured according to the approach of itself known by mixing in ordinary use, granulation, coating, the dissolution, or the freeze drying method, and, in the case of a freeze-drying object, the drugs of this invention contain the active substance to about 100 % about 0.1 %-100 %, especially about 1% to 50%.

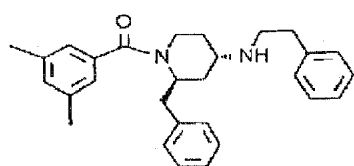
[0082] This invention relates also to utilization of the compound of Formula I in the form of drugs preferably again. It will depend for a dosage on various factors, for example, the format of administration, a kind, age, and/or an individual condition. The daily doses which should be prescribed for the patient are about 0.25 - about 10 mg/kg in internal use, and are about 70 kg preferably. They are about 20 mg - about 500 mg about the homeotherm which has weight. The following example is for explaining this invention. Temperature is given with a Celsius degree and a pressure is given by the millibar (mbar).

[0083] Example 1: (2R, 4S) and (2R, 4R) -2-benzyl-1-(3, 5-dimethylbenzoyl)-N-(2-phenethyl)-4-piperidine amine hydrochloride 1.26 g (17.1 millimol) Hydrogenation cyano boron sodium (85%) is divided. It crosses in 10 minutes and is 30 ml. 3.65 g in a methanol (11.4 millimol) (2R, 4RS)-2-benzyl-1-(3, 5-dimethylbenzoyl)-4-piperidine amine, 935 mg (11.4 mols) Sodium acetate and 0.65 ml (11.4 mol) An acetic acid and 1.44 g (12 millimol) In 0 degree C, it adds under nitrogen into the mixture of phenylacetaldehyde. Subsequently, a reaction mixture is stirred at a room temperature for 3 hours, and also it is 0.376 g (2.4 millimol).

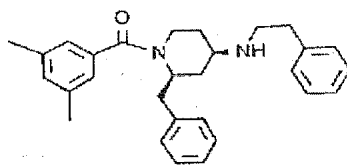
Phenylacetaldehyde was added and stirring was continued at 4 degrees C for 16 hours. A methanol is removed in a rotary evaporator and the reaction mixture of band red is made to distribute between the ether and 1-N sodium-hydrogencarbonate solution. An organic phase is washed by brine, and evaporation to dryness is dried and carried out on a sodium sulfate. The mixture of the hydrochloride of the bottom-type object compound is obtained as yellow oil.

[0084]

[Formula 40]



ジアステレオマー A



ジアステレオマー B

[0085] They are a methylene chloride / methanol / dark ammonia about this. (97.5:2.25:0.25) If chromatography processing is carried out on silica gel using eluate mixture and a diastereomer is separated, a diastereomer will be obtained as the pure free base.

TLC : Methylene chloride/methanol (98:2) Diastereomer A(R [ 2 ], 4R):Rf =0.16; melting point 248-249 \*\*: [α]<sub>D</sub> = -56.9 degree (c= 0.946, methanol); MS: M<sup>+</sup> = 426 (free base).

Diastereomer B(2R, 4S): Rf =0.06; melting point 270 \*\*: (decomposition); [α]<sub>D</sub> = +30.6 degree (c= 0.759, methanol); MS: M<sup>+</sup> = 426 (free base).

Starting material for this is prepared as follows.

[0086] a) The inside of the methanol of (R)-3-benzylamino-4-phenyl ethyl-butylate 400 ml, 42.2 g obtained according to esterification of the known (R)-3-amino-4-phenyl butanoic acid in ethanol (0.203 mol) (R)-3-amino-4-phenyl ethyl butylate, 11.6 ml (0.203 mols) A glacial acetic acid and 33.3 g (0.406 mol) Sodium acetate and 20.9 ml (0.207 mols) In the solution of a benzaldehyde It is hydrogenation cyano boron sodium (0.304 mols) of 19.1 g at all. Division addition is carried out in -5 degrees C - 5 degrees C. A reaction is made to complete at a room temperature after termination of addition for 1 hour. Yellow suspension is condensed nearly thoroughly in a rotary evaporator, and paste-like residue is made to distribute between ethyl acetate and the water adjusted to abbreviation pH 8 with ammonia liquor. An organic phase is washed until water and brine form neutrality, evaporation to dryness is dried and carried out on magnesium sulfate, and yellow oil is obtained. They are a methylene chloride/methanol about this. (99:1) If it uses and chromatography processing is carried out on silica gel, the object compound will be obtained as light yellow oil. An oxalate is obtained by adding oxalic acid to the ether solution of this object compound.

[0087] Melting point: 142-143 \*\*: TLC : A methylene chloride/methanol (95:5) :Rf =0.63 MS: M<sup>+</sup> - 91 = 206 [(60 %) α]<sub>D</sub> = +3 \*\*: (c= 1, ethanol) [free base α]<sub>D</sub> = -0.8 \*\*: (c= 1 and CHCl<sub>3</sub>) oxalate C<sub>21</sub>H<sub>25</sub>NO<sub>6</sub>:(oxalate) C Calculated value 65.11%, actual measurement 65.12% H Calculated value 6.51%, actual measurement 6.46% N Calculated value 3.62%, actual measurement 3.77%

[0088] b) 43.8 ml in the toluene of (R)-N-benzyl-N-[(1-ethoxy carbonylmethyl-2-phenyl) ethyl] carbamoyl methyl-acetate 480 ml (0.408 mols) It is the solution of methyl malonyl chloride 2.5 It crosses to time amount. 115.8 g in the toluene of 630 ml (0.389 mols) (R)-3-benzylamino-4-phenyl ethyl butylate, 56.8 ml (0.408 mols) Dropping addition is carried out so that temperature may be maintained within 0-5 degrees by the ice-cooling solution of triethylamine and the dimethylamino pyridine of 366 mg. This suspension is

made to react thoroughly for 2 hours, and, subsequently to the iced water of 500 ml, is poured out. an organic phase is separated -- sequential washing is carried out by the 0.1N solution of hydrochloric acid, 1-N sodium-hydrogencarbonate solution, and iced water, and, subsequently evaporation to dryness is dried and carried out on a sodium sulfate. About the obtained yellow oil, they are ethyl acetate/hexane. (1:2) The object compound will be obtained if the chromatography on the used silica gel refines.

TLC : Ethyl acetate/hexane (1:2) :Rf =0.25 MS:M+=397 [(3%) alpha] D =+19.5 degree (c= 1.3, CHCl3)

[0089] c) (6R) -1, 6-dibenzyl -2, The 4-dioxo-3-piperidine carboxylic-acid methyl 520 53.9 in the tert-butanol of ml g (0.135 mol) It is 15.2 g (0.135 mol) at a room temperature to the solution of (R)-N-benzyl-N-[(1-ethoxy carbonylmethyl-2-phenyl) ethyl] carbamoyl methyl acetate.

Potassium tert-swine NORATO is added. It is made to react thoroughly for 1 hour. Light yellow suspension is set to a room temperature, and it is 1Eq (8.1g). It mixes with a glacial acetic acid, and condenses to the capacity of about 100 ml. This concentrate is diluted with 300ml water, and the ethyl acetate of each time 300 ml extracts 3 times. Sequential washing of the organic phase is carried out by water and brine, and it uses for the next phase, without obtaining the object compound of transparent yellow oil and refining this further, if evaporation to dryness of the organic phase subsequently doubled is dried and carried out on a sodium sulfate. Ethyl acetate/methanol (1:1) :Rf =0.3.

[0090] d) The toluene of (6R)-1, the 6-dibenzyl -2, and 4-piperidine dione 298 ml, and 10% of 445 ml (v/v) 106.1 g in an acetic acid (0.301 mols) (6R) It is the solution of -1, the 6-dibenzyl -2, and 4-dioxo-3-piperidine carboxylic-acid methyl at 80 degrees 2.5 Time amount heating is carried out. It neutralizes by adding the solid-carbon-dioxide sodium of 48 g, cooling a reaction mixture to a room temperature and cooling by iced water, and a phase is separated, and the ethyl acetate of 300 ml extracts the aqueous phase once again. The doubled organic phase is washed with water, subsequently it washes by brine, and evaporation to dryness is dried and carried out on a sodium sulfate. The object compound will be obtained if the obtained oil is crystallized from the ether.

Melting point: 97-97.5 \*\*TLC : Ethyl acetate/hexane (2:1) :Rf =0.31[alpha] D =+166.9 \*\* (c= 1 and CHCl3)

MS:M+=293 [(2.4%)0091] e) -- a (2R, 4RS)-1 and 2-dibenzyl-4-piperidine amine strange method -- e1e1a(6R)-1 and 6-dibenzyl-4-(methoxy imino)-2-piperidone 68 ml 10 g (0.034 mol) In a pyridine It is 3.09 g (0.037 mol) about the solution of \*\* (6R) -1, the 6-dibenzyl -2, and 4-piperidine dione. It mixes with a methoxy amine hydrochloride and heats at 85 degrees for 1 hour. 1N solution of hydrochloric acid (pH 3 [ about ]) of ice-cooling is filled with a transparent yellow solution, and it extracts with toluene. If evaporation to dryness is dried and carried out on a sodium sulfate after carrying out sequential washing of the organic extract by 1-N solution

of hydrochloric acid, 1-N sodium-carbonate solution, and brine, the object compound will be obtained in the form of a wax-like crystal.

Melting point: 63-77 °C; TLC : Ethyl acetate/hexane (1:1) :R<sub>f</sub> =0.52; MS:M<sup>+</sup>=322 (1.4%).

According to <sup>1</sup>H-NMR (CDCl<sub>3</sub>), it is abbreviation. Singh / anti mixture exists by the ratio of 7:3, and the methoxy signal of this oxime ether exists in 3.92 and 3.88 ppm.

[0092] e1b(2R, 4RS)-1 and 2-dibenzyl-4-piperidine amine 90 ml 9.19 g in a tetrahydrofuran (0.0285 mols) (6R) The condensator and Vigreux to which 40-degree C water flows the solution of -1 and 6-dibenzyl-4-(methoxy imino)-2-piperidone It is made to heat and flow back under an argon in the distillation apparatus furnished with a column. It crosses to this solution in 20 minutes, and is 6.1 ml (0.0643 mols). Dropping addition of borane / the dimethyl sulfide complex is carried out, and subsequently to 4 hours it crosses, and is 9 ml (0.0949 mols). Dropping addition of the two-times eye of borane / dimethyl sulfide complex is performed. The dimethyl sulfide which separated during addition of borane / dimethyl sulfide complex is removed through a distillation apparatus.

[0093] If addition is completed, it will be during an iced water bath, a reaction mixture will be cooled at 0-4 degrees, and superfluous borane will be hydrolyzed by adding the methanol of 20 ml slowly in all. After intense febrile hydrolysis is suppressed, a solvent is directly removed from this distillation apparatus under a water jet pump vacuum. Subsequently, it is 90 ml to residue. It boils for 2 hours, after adding 5-N solution of hydrochloric acid. By cooling this solution to a room temperature and diluting with the water of 200 ml, the ether extracts, acidity and a neutral part are removed, subsequently, it is during an iced water bath, the aqueous phase is cooled, 5-N sodium-hydroxide solution adjusts to abbreviation pH 9, and they are the ether/tetrahydrofuran about a base part. (2:1) It extracts. If evaporation to dryness of the organic extract is dried and carried out on magnesium sulfate, a raw salt radical will be obtained in the form of yellowish oil. This is used for the next phase as it is. TLC : A methylene chloride / methanol / dark ammonia (90:10:0. 4) :R<sub>f</sub> =0.3. It dissolves into the methanolic solution of hydrochloric acid, and the amorphous dihydrochloride of the object compound precipitates by adding the ether. Melting point 150 to 182 °C.

[0094] a strange method -- 30 g in e2e2a(6R)-1, the 6-dibenzyl -2, and the toluene of 4-piperidine dione 4-ethylene ketal 800 ml (0.102 mol) (6R)-1, the 6-dibenzyl -2, 4-piperidine dione, and 50 ml Ethylene glycol and 1.8 g The solution of p-toluenesulfonic-acid monohydrate is heated for 3 hours using a water separator. This solution is cooled to a room temperature and it washes by 1-N sodium-hydrogencarbonate solution and brine of 100 ml, and if evaporation to dryness of the organic phase is dried and carried out on magnesium sulfate, rough ketal will be obtained as oil. The chromatography on the silica gel using ethyl acetate refines this, and if the oil obtained from this chromatography is crystallized from the ether, the object compound will be obtained in the form of a white crystal. Melting point: 91-93 °C; TLC :

Ethyl acetate/hexane (3:1) :Rf =0.53;MS:M+=337.

[0095] 10.2 g in e2b (2R) -1 and the tetrahydrofuran of 2-dibenzyl-4-piperidone ethylene ketal 100 ml (0.0302 mols) (6R) in the solution of -1, the 6-dibenzyl -2, and 4-piperidine dione 4-ethylene ketal It crosses in 10 minutes under an argon, and is 7.6 ml (0.0756 mols). Borane / dimethyl sulfide complex is added, mixture is heated, and it is made to flow back for 1 hour. Subsequently, a solution is cooled to a room temperature and it is 40 ml. Add 2-N sodium-hydroxide solution, and heat for 2 hours, it is made to flow back again, and, subsequently a tetrahydrofuran is removed in a rotary evaporator. The ether extracts a reaction mixture, a sodium hydrogencarbonate washes an organic extract, and the object compound will be obtained if evaporation to dryness is dried and carried out on magnesium sulfate. TLC : Ethyl acetate/hexane (2:1) :Rf =0.81;MS:M+=323.

[0096] e2c(2R)-1, and dioxane of 2-dibenzyl-4-piperidone 170 ml and 1000 ml 85.7 g in the 2.25M solution of hydrochloric acid (0.261 mol) (2R) The solution of -1 and 2-dibenzyl-4-piperidone ethylene ketal is heated at 70 degrees C for 29 hours. Subsequently, it removes under reduced pressure of dioxane, and a sodium-hydroxide solution adjusts the aqueous phase to abbreviation pH 8 30%, cooling by iced water, and the ether extracts. 1-N sodium-hydrogencarbonate solution washes an ether extract, and if evaporation to dryness is dried and carried out on a sodium sulfate, the object compound will be obtained as oil which redness cut. Since this is unstable, it performs the next phase, without refining. TLC : Ethyl acetate/hexane (1:1): Rf =0.71;FD-MS : M+=279.

[0097] e2d(2R)-1 and 2-dibenzyl-4-(methoxy imino) piperidine 3 g (0.01071 mols) (2R) -1, 2-dibenzyl-4-piperidone, and 4.4g (0.0537 mol) Sodium acetate and 942 mg (0.0113 mols) It is 30 ml about a methoxy amine hydrochloride. It dissolves in ethanol and this suspension is heated for 30 minutes at 60 degrees C. Subsequently, remove under reduced pressure of ethanol and residue is made to distribute between water and ethyl acetate, and a rough product will be obtained if evaporation to dryness of the organic phase is dried and carried out on a sodium sulfate. They are ethyl acetate/hexane about this. (3:1) If the chromatography on the used silica gel refines, the object compound will be obtained in the form of oil.

TLC : Ethyl acetate/hexane (1:1) : Rf 1= 0.84, Rf 2= 0.76 (Singh / anti oxime ether);  
MS:M+ =308 (1%), M+ -91=217 (90 %);

1 H-NMR spectrum (CD3OD), delta (ppm) = 3.85 (s, =N-OCH3), and 3.825 (s): About 1:1.

[0098] e2e(2R, 4RS)-1, 2-dibenzyl-4-piperidine amine - 78-degree 60 ml 5.43 g in a tetrahydrofuran (17.6 millimol) (2R) Gas ammonia dried on the potassium hydroxide in the solution of a -1 and 2-dibenzyl-4-(methoxy imino) piperidine 180 ml It introduces. In this solution, it sets at -70 degrees, and is 3.7 g (69 millimol). An ammonium chloride and 1.6 g (70.4 millimol) Division addition of the metallic sodium is carried out. the suspension produced 1 hour after -- further -- 3.7 g An ammonium chloride and 0.6 g Metallic sodium is added and,



subsequently this is stirred in -70 degrees for 2 hours. Subsequently, a cooling bath is removed and gas ammonia is evaporated. If make residue distribute between 1-N sodium-hydroxide solution and the ether, an organic phase is separated, back extraction of the aqueous phase is carried out, an organic phase is washed by brine and evaporation to dryness of the doubled organic and phase is dried and carried out on a sodium sulfate, the object compound will be obtained in the form of yellow oil.

TLC : A methylene chloride / methanol / dark ammonia (90:9:1) :  $R_f = 0.33$ ; MS:  $M^+ = 280$ .

[0099] f) (2R, 4RS)-N- (1, 2-dibenzyl-4-piperidyl) 20 ml put into the trifluoro acetamide trifluoroacetic acid salt iced water bath 6.88 g in a methylene chloride (24.5 millimol) In the solution of (2R, 4RS)-1 and 2-dibenzyl-4-piperidine amine 5.1 ml (36.8 millimol) A trifluoroacetic acid anhydride is added and, subsequently stirring is continued at a room temperature for 1 hour. If evaporation to dryness of the reaction mixture is carried out, the object compound will be obtained as light yellow form. TLC : A methylene chloride / methanol / dark ammonia (190:9:1) :  $R_f = 0.41$  (cis-) and 0.57 (transformer) diastereomer; MS:  $M^+ - 91$  (benzyl) = 285 (14 %).

[0100] g) (2R, 4RS)-N- (2-dibenzyl-4-piperidyl) 19.3 g in the dioxane of trifluoro acetamide trifluoroacetic acid salt 160 ml (39.4 millimol) (2R --) It is 3.0 g under nitrogen to the solution of a 4RS-N-(1, 2-dibenzyl-4-piperidyl) trifluoro acetamide trifluoroacetic acid salt. 10% palladium / carbon catalyst is added, and it hydrogenates in a room temperature under atmospheric pressure. A reaction mixture is filtered on Celite™, a catalyst is removed, and residue is washed by dioxane. It is used without obtaining the object compound and refining this further, if evaporation to dryness of the filtrate is carried out and it dries under a high vacuum.

TLC : A methylene chloride / methanol / dark ammonia (90:9:1) :  $R_f = 0.24$  (two diastereomers separated slightly).

[0101] h) 3 of the solid-carbon-dioxide hydrogen sodium of (2R, 4RS)-N-[2-benzyl-1-(3, 5-dimethylbenzoyl)-4-piperidyl] trifluoro acetamide 710 mg, and 712 mg, and 5-dimethylbenzoyl chloride 1.39 g cooled by iced water (3.44 millimol) A (2R, 4RS)-N-(2-dibenzyl-4-piperidyl) trifluoro acetamide trifluoroacetic acid salt and 10 ml Toluene/water (1:1) It adds into stirring mixture. Subsequently, after warming a reaction mixture to a room temperature, it stirs for 2 hours and is made to distribute between toluene and 1-N sodium-hydrogencarbonate solution. An organic phase is washed with water, and evaporation to dryness is dried and carried out on magnesium sulfate. colorless oil -- ethyl acetate/hexane (1:2) using -- a silica gel top -- the object compound will be obtained if chromatography processing is carried out. It is used without refining this further.

TLC : A methylene chloride / methanol / dark ammonia (190:9:1) :  $R_f = 0.5$  (two diastereomers are not separated under these conditions).

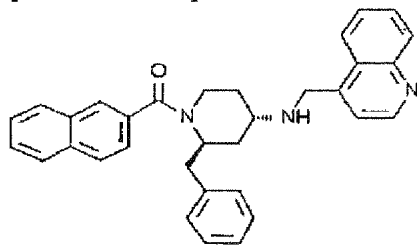
MS:  $M^+ = 418$  (14 %)  $M^+ - 91 =$  (43 %).

[0102] i) (2R, 4RS)-2-benzyl-1-(3 and 5-dimethylbenzoyl)-4-piperidine amine 50 ml A tetrahydrofuran/methanol (1:1) In the solution of the (2R, 4RS)-N-[2-benzyl-1-(3, 5-dimethylbenzoyl)-4-piperidyl] trifluoro acetamide of inner 4.73 g (10.4 millimol) In a room temperature, 5-N sodium-hydroxide solution of 4.1 ml is added under nitrogen, this mixture is heated, and it is made to flow back for 3 hours. After a reaction is completed, a reaction mixture is cooled in iced water, and it adjusts to abbreviation pH 1 by 1-N solution of hydrochloric acid, and an organic solvent is removed in a rotary evaporator. It is abbreviation pH 10 by adding 10-N sodium-hydroxide solution, the ether extracting the acid aqueous phase which remained first, removing acidity and a neutral part, and cooling in iced water subsequently. It adjusts and the ether extracts. An organic phase is washed by brine, and if evaporation to dryness is dried and carried out on a sodium sulfate, the free base is obtained as brown oil, and it will be used, without refining this further. TLC : A methylene chloride / methanol / dark ammonia (90:9:1) :  $R_f = 0.29$ ; MS:  $M^+ = 322$  (0.03 %)  $M^+ - 91 = 231$  (62 %). L-phenyl ARANI Norian is left according to the above-mentioned reaction sequence, and -(2S, 4RS)-2-benzyl-1-(3, 5-dimethylbenzoyl)-4-piperidine amine is obtained similarly.

[0103] Example 2: (2R\* and 4S\*) -2-benzyl-1-(2-naphthoyl)-N-(4-quinolyl methyl)-4-piperidine amine 28 mg (0.73 millimol) A sodium borohydride is set at 0 degree over for 20 minutes in 3 steps. 106 mg in the methanol of 1.5 ml (0.182 RIMORU) It adds in the solution of (2R\* and 4S\*)-2-benzyl-1-(2-naphthoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. Subsequently, this mixture is stirred at 0 degree for 3 hours. Subsequently, it is 0.06 ml (0.81 millimol) to a reaction mixture. It stirs for 10 minutes by adding an acetone. A methanol is removed in a rotary evaporator and solid white residue is made to distribute between ethyl acetate and water. An organic phase is washed by brine, and evaporation to dryness is dried and carried out on magnesium sulfate. They are a methylene chloride / methanol / dark ammonia about the obtained white form. (1500:50:1) It uses and chromatography processing is carried out on silica gel. The bottom-type object compound is obtained as white form.

[0104]

[Formula 41]



[0105] TLC : A methylene chloride / methanol / dark ammonia (700:50:1) :  $R_f = 0.34$ ; FD-MS :  $M^+ = 485$ .

[0106] A start compound for this is prepared as follows.

a) The 2-benzyl-N-benzyloxycarbonyl -2, 3-dihydro - 4 -(1H)- Pyridone 165 ml (1.16 mols) Benzyl chloro formate is set at -70 degrees under an argon over for 20 minutes, and it is 1 L. 104 g in an anhydrous tetrahydrofuran (0.95 mol) Dropping addition is carried out at the solution of 4-methoxy pyridine. The suspension of a thick beige color is diluted with the anhydrous tetrahydrofuran of 200 ml. this reaction mixture -- three-mol benzyl chloride solution in absolute ether 460 ml (1.46 mol) Magnesium waste in the absolute ether of 160 ml 35.5 g (1.46 mol) from -- dropping addition of the prepared Grignard reagent is carried out over for 75 minutes, maintaining temperature at -70 degrees. Furthermore, it is warmed to a room temperature after 10 minutes. It is diluted with the ether of 500 ml, dropping addition of the 4-N hydrochloric acid of 900 ml is carried out, and a phase is separated. An organic phase is washed by water and brine, and evaporation to dryness is dried and carried out on magnesium sulfate. They are a hexane/ethyl acetate about residue. (3:1) Chromatography processing is used and carried out. The object compound is obtained as viscous colorless oil. TLC : Hexane/ethyl acetate (1:3) :Rf =0.7 ; IR: 1725, 1665, 1602 cm<sup>-1</sup>.

[0107] b) (2R\* and 4R\*)-2-benzyl-4-hydroxy piperidine 1.5 L 150 g in a methanol (0.467 mols) The 2-benzyl-N-benzyloxycarbonyl -2, 3-dihydro - 4 -(1H)- pyridone as a catalyst -- 7.5 g Pd/C (10%) using -- hydrogenating -- subsequently -- Raney of 50 g nickel -- and -- further -- the methanol of 200 ml is added and hydrogenation is advanced thoroughly. They are a methylene chloride / methanol / dark ammonia about the brown oil which was made to evaporate in a rotary evaporator and was obtained after filtering. (60:10:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as a merocrystalline lump, and it is used, without refining this further. The white crystal of the melting point of 111-112 \*\* is obtained by crystallization of the sample from the ether/hexane. TLC : A methylene chloride / methanol / dark ammonia (40:10:1) Rf=0.55;FD-MS : M+=191.

[0108] c) 28 g in the chloroform of (2R\* and 4R\*)-2-benzyl-1-t-butyloxy carbonyl-4-hydroxy piperidine 500 ml (146 millimol) A (2R\* and 4R\*)-2-benzyl-4-hydroxy piperidine and 35.1 g (161 millimol) The solution of G tert-butyl dicarbonate is stirred in 50 degrees for 20 hours. Subsequently, it is condensed in a rotary evaporator and they are a methylene chloride / methanol / dark ammonia about yellow oil. (2000:50:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (2000:50:1) Rf =0.43;FD-MS : M+=291.

[0109] d) (2R\* and 4R\*)-2-benzyl-1-t-butyloxy carbonyl-4-methane sulfonyloxy hydroxy piperidine 33.3 ml (428 millimol) Methane sulfonyl chloride It is 75 ml, cooling in ice. 62.4 g in a pyridine (214 millimol) Dropping addition is carried out at the solution of a (2R\* and 4R\*)-2-benzyl-1-t-butyloxy carbonyl-4-hydroxy piperidine. Stirring of suspension is continued at a room temperature after 30 minutes by 0 degree for further 3 hours. After condensing in a rotary evaporator, a reaction mixture is washed by ejection, water, and brine in ethyl acetate, and it

dries on magnesium sulfate, and is made to evaporate in a rotary evaporator. The object compound crystallizes as a white crystal from the ether. Melting point: 110-115 °C; TLC : Toluene/ethyl acetate (4:1) R<sub>f</sub> = 0.42; FD-MS : M<sup>+</sup> = 369.

[0110] e) () [ 2R\*, ] [ 4S\* ] -2-benzyl-1-t-butyloxy carbonyl-4-piperidine azide 98.9 g (267 millimol) (2R\* and 4R\*)-2-benzyl - 1-t-butyloxy carbonyl-4-methane sulfonyloxy hydroxy piperidine, 14.4g (294 millimol) A horse mackerel-ized lithium and the mixture of the N,N-dimethylformamide of 500 ml are stirred at 80 degrees under an argon for 3 hours. A reaction mixture is diluted with ethyl acetate, it washes by water and brine, and evaporation to dryness is dried and carried out on magnesium sulfate. Considering the obtained brown oil as an eluate, they are toluene/ethyl acetate. (9:1) It uses and chromatography processing is carried out on silica gel. The object compound is 2-benzyl-N-t-butyloxy carbonyl. - It is obtained in mixture with a 1, 2, 5, and 6-tetrahydro pyridine (weight ratio = [ according to 1 H-NMR ] 4.2:1), and this is used without classifying further. TLC : Toluene/ethyl acetate (9:1) R<sub>f</sub> = 0.59; FD-MS : M<sup>+</sup> = 316 ; IR: 2100, 1685 cm<sup>-1</sup>.

[0111] f) () [ 2R\*, ] [ 4S\* ] -2-benzyl - 4.16 g in the methanol of 1-t-butyloxy carbonyl-4-piperidine amine 100 ml (13.1 millimol) (2R\* and 4S\*)-2-benzyl-1-t-butyloxy carbonyl-4-piperidine azide and 0.99 g (3.62 millimol) 2-benzyl-N-t-butyloxy carbonyl - They are hydrogen and 1g about the mixture (what was calculated based on 1 H-NMR spectrum) of a 1, 2, 5, and 6-tetrahydro pyridine. It hydrogenates using Pd/C 10%. When incorporation of hydrogen is completed, you filter mixture and make it evaporate in a rotary evaporator. About the obtained brown oil, they are a methylene chloride / methanol / dark ammonia. (350:50:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (350:50:1) R<sub>f</sub> = 0.4; FD-MS : M<sup>+</sup> = 290.

[0112] g) 5 g in toluene (17.2 millimol) (2R\* and 4S\*)-2-benzyl-1-t-butyloxy carbonyl-N-(4-quinolyl methyl)-4-piperidine amine 50 ml () [ 2R\*, ] [ 4S\* ] -2 - Benzyl-1-t-butyloxy carbonyl-4-piperidine amine and 2.7 g (17.2 millimol) The mixture of a quinoline-4-carboxy aldehyde is stirred at a room temperature. 2 hours after and 2.8 g (23.3 millimol) Sulfuric anhydride magnesium is added. Mixture is filtered 16 more hours after and filtrate is condensed. It is 50 ml about brown oil. It melts to a methanol and is 0.69 g (18.3 millimol). A sodium borohydride is added in 4 steps. After stirring at a room temperature for 3 hours, a reaction mixture is condensed and it washes by ejection, water, and brine in ethyl acetate. Evaporation to dryness of the organic phase is dried and carried out on magnesium sulfate. About the obtained brown oil, they are a methylene chloride / methanol / dark ammonia (850:50:1). It uses and chromatography processing is carried out on silica gel. The object compound is obtained in the form of yellow oil. TLC : a methylene chloride / methanol / dark ammonia (700:50:1) -- R<sub>f</sub> = 0.38; FD-MS : M<sup>+</sup> = 431.

[0113] h) (2R\* and 4S\*)-2-benzyl-1-t-butyloxy carbonyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 2.2 ml (15.8 millimol) A trifluoroacetic acid anhydride It sets at 0 degree under an argon. 60 ml 6.2 g in a methylene chloride (14.4 Millimol) (2R\* and 4S\*)-2-benzyl-1-t-butyloxy carbonyl-N-(4-quinolyl methyl)-4-piperidine amine and 2.6 ml (18.7 millimol) It adds in the solution of triethylamine. And a reaction mixture is stirred at 0 degree for 3 hours. It is diluted with a methylene chloride and washed with water. Evaporation to dryness of the organic phase is dried and carried out on magnesium sulfate. The object compound is TLC. It is obtained in the form of yellow oil as a pure product. TLC : A methylene chloride / methanol / dark ammonia (700:50:1) Rf =0.62;DCI-MS:(M+H)+=528.

[0114] i) -- (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-, cooling in N-trifluoro acetyl-4-piperidine amine ice 7.73 g (14.7 millimol) To (2R\* and 4S\*)-2-benzyl-1-t-butyloxy carbonyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 6-N hydrogen chloride in dioxane 250 ml Dropping addition is carried out over for 3 minutes, and, subsequently this mixture is stirred at a room temperature for 1 hour. A reaction mixture is condensed in a rotary evaporator, and it is made basicity with 1-N sodium-hydrogencarbonate solution, and a methylene chloride extracts. Evaporation to dryness of the organic phase is dried and carried out on magnesium sulfate. About the obtained brown oil (7.14 g), they are a methylene chloride / methanol / dark ammonia. (850:50:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (700:50:1) Rf =0.42;DCI-MS:(M+H)+=428 ; IR:1690 cm<sup>-1</sup>.

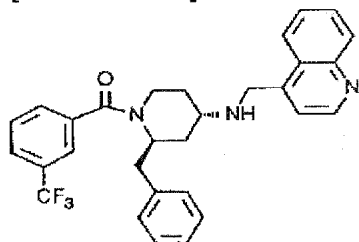
[0115] j) 97 mg in the toluene of (2R\* and 4S\*)-2-benzyl-1-(2-naphthoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 1 ml (0.56 millimol) In the solution of 2-naphthoic acid In 50 degrees, it crosses in 10 minutes under an argon, and is 58microl in the toluene of 0.2 ml (0.795 millimol). Dropping addition of the solution of thionyl chloride is carried out, and a reaction mixture is stirred at 80 degrees for 2 hours. Subsequently, it is condensed in a rotary evaporator, the toluene of 1 ml is added, and evaporation is repeated twice. Brown oil is melted in the methylene chloride of 1 ml, and it is 200 mg (0.468 millimol) under an argon to this. The solution of (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine is added at 0 degree, and it stirs at 0 degree for 2 hours. Subsequently, water is added to a reaction mixture and a methylene chloride extracts. An organic phase is washed by brine, and evaporation to dryness is dried and carried out on magnesium sulfate. About the obtained yellow oil, they are a methylene chloride / methanol / dark ammonia. (1000:50:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (2000:50:1) Rf =0.36;FD-MS : M+=581.

[0116] It is made to be the same as that of the Example 3:(2R\* and 4S\*)-2-benzyl-1-(3-trifluoromethyl benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 0.184 g (0.307

millimol) It is 0.046 g (1.23 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(3-trifluoromethyl benzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as yellow oil.

[0117]

[Formula 42]



[0118] TLC : A methylene chloride / methanol / dark ammonia (700:50:1) R<sub>f</sub> =0.28;FD-MS : M<sup>+</sup>=503.

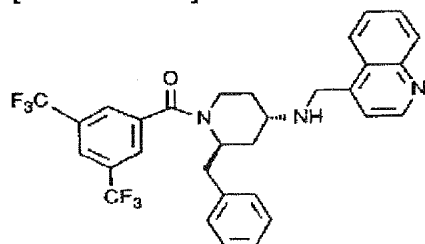
[0119] A start compound for this is prepared as follows.

(2R\* and 4S\*)-2-benzyl-1-(3-trifluoromethyl benzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 2j It is made the same. 106 mg (0.56 millimol) It is 58microl (0.795 millimol) first about 3-trifluoromethyl benzoic acid. You make it react with thionyl chloride. Subsequently, 200 mg (0.468 millimol) You make it react with (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine, and the object product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1) R<sub>f</sub> =0.56;FD-MS : M<sup>+</sup>=599.

[0120] It is made to be the same as that of the Example 4:(2R\* and 4S\*)-2-benzyl-1-[3 and 5-bis(trifluoromethyl) benzoyl]-N-(4-quinolyl methyl)-4-piperidine amine example 2. 0.271 g (0.406 millimol) (2R\* and 4S\*)-2-benzyl-1-[3 and 5-bis(trifluoromethyl) benzoyl]-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 0.061 g (1.23 millimol) It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0121]

[Formula 43]



[0122] TLC : A methylene chloride / methanol / dark ammonia (1000:50:1) R<sub>f</sub> =0.21;FD-MS : M<sup>+</sup>=571.

[0123] A start compound for this is prepared as follows.

(2R\* and 4S\*)-2-benzyl-1-[3 and 5-bis(trifluoromethyl) benzoyl]-N-(4-quinolyl methyl)-N-trifluoro

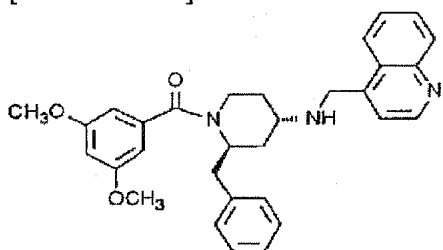
acetyl-4-piperidine amine 143 mg (561 millimol) \*\* bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 144 mul (1.03 millimol) Triethylamine 200 mg in the methylene chloride of 3 ml (467 Millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine and 113 mg (561 millimol) It adds in the solution of a 3 and 5-bis(trifluoromethyl) benzoic acid. And a reaction mixture is stirred at a room temperature for 16 hours.

Subsequently, it is diluted with a methylene chloride, sequential washing of the organic phase is respectively carried out by a unit of 1 time by the citric acid, 1-N sodium-hydrogencarbonate solution, and brine 10%, and evaporation to dryness is dried and carried out on magnesium sulfate. About the form which the yellow taste cut, they are a methylene chloride / methanol / dark ammonia. (1000:50:1) It uses and chromatography hula fee processing is carried out on silica gel. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (1000:50:1) Rf =0.34;FD-MS : M+=667.

[0124] It is made to be the same as that of the Example 5:(2R\* and 4S\*)-2-benzyl-1-(3, 5-dimethoxybenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 250 mg (0.423 millimol) It is 64 mg (1.69 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(3, 5-dimethoxybenzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0125]

[Formula 44]



[0126] TLC : A methylene chloride / methanol / dark ammonia (1000:50:1) Rf =0.23;DCI-MS: (M+H)+=496.

[0127] A start compound for this is prepared as follows.

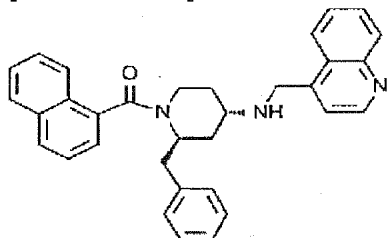
It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(3, 5-dimethoxybenzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 4. 200 mg (0.467 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 102 mg (0.561 millimol) 3, 5-dimethoxy benzoic acid, 143 mg (0.561 millimol) Bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 144 mul (1.03 millimol) It is made to react with triethylamine. The object compound is obtained as white form. TLC : A methylene chloride / methanol / dark ammonia (1000:50:1) Rf =0.31;FD-MS : M+=591.

[0128] It is made to be the same as that of the Example 6:(2R\* and 4S\*)-2-benzyl-1-(1-naphthoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 200 mg (0.344 millimol) It is 52

mg (1.37 millimol) about  $^{**}$  (2R\* and 4S\*)-2-benzyl-1-(1-naphthoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0129]

[Formula 45]



[0130] TLC : A methylene chloride / methanol / dark ammonia (1000:50:1)  $R_f$  = 0.35; FD-MS :  $M^+$  = 485.

[0131] A start compound for this is prepared as follows.

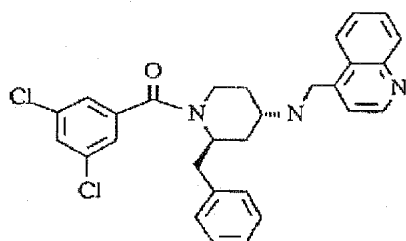
(2R\* and 4S\*)-2-benzyl-1-(1-naphthoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 92 microl (0.655 millimol) 1-chloro - N, N, and a 2-trimethyl-1-propene-1-amine It sets at 0 degree and is 96 mg in the desiccation methylene chloride of 2 ml (0.561 millimol). It adds in the solution of 1-naphthoic acid, and, subsequently this mixture is stirred at a room temperature by 0 degree for 1 hour for 1 hour. And it is 200 mg in the methylene chloride of 3 ml (0.468 millimol) to this obtained yellow solution. (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine and 130 mul (0.936 millimol) In a room temperature, dropping addition of the solution of triethylamine is carried out over for 10 minutes. After stirring at a room temperature for 3 hours, water is added, and an organic phase is separated and it washes twice [ further ] with water. Evaporation to dryness of the organic phase is dried and carried out on magnesium sulfate. About the obtained yellow oil, they are a methylene chloride / methanol / dark ammonia. (800:50:1) It uses and chromatography hula fee processing is carried out on silica gel. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  = 0.49; FD-MS :  $M^+$  = 581.

[0132] It is made to be the same as that of the Example 7: (2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 1.21 g (2.01 millimol) ( ) [ 2R\*, ] [ 4S\* ] It is 0.305 mg (8.06 millimol) about -2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0133]

[Formula 46]





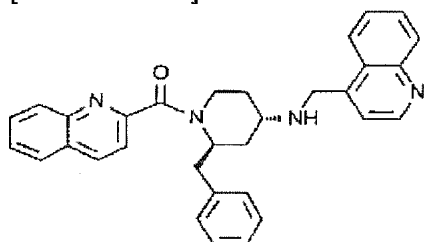
[0134] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.37;FD-MS :  $M^+$ =503. A start compound for this is prepared as follows.

[0135] (2R\* and 4S\*)-2-benzyl-1-(3, 5-dichlorobenzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 2j It is made the same. 1.11 g (5.85 millimol) It is 0.63 ml (8.77 millimol) first about 3 and 5-dichloro benzoic acid. You make it react with thionyl chloride. Subsequently, 1 g (2.34 millimol) You make it react with (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine, and a product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$ =0.65;FD-MS :  $M^+$ =599.

[0136] It is made to be the same as that of the Example 8:(2R\* and 4S\*)-2-benzyl-1-(2-KINORI nil carbonyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 155 mg (0.266 millimol) \*\* (2R\* and 4S\*)-2-benzyl-1-(2-KINORI nil carbonyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine is made to react with the sodium borohydride of 40 mg (1.06 millimol). The bottom-type object compound is obtained as white form.

[0137]

[Formula 47]



[0138] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.42;FD-MS :  $M^+$ =486.

[0139] A start compound for this is prepared as follows.

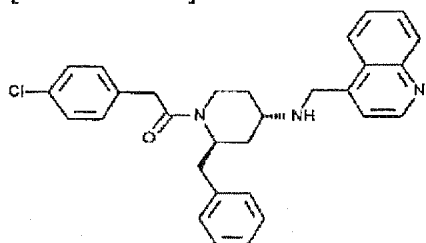
(2R\* and 4S\*)-2-benzyl-1-(2-KINORI nil carbonyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 2j It is made the same. 97 mg (0.56 millimol) It is 58microl (0.795 millimol) first about a quinoline-2-carboxylic acid. You make it react with thionyl chloride. Subsequently, 200 mg (0.468 millimol) You make it react with (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine, and a product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.45;FD-MS :  $M^+$ =582.

[0140] It is made to be the same as that of the Example 9:(2R\* and 4S\*)-2-benzyl-1-(4-

chlorophenyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 256 mg (0.441 millimol) It is 66 mg (1.76 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(4-chlorophenyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0141]

[Formula 48]



[0142] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$ =0.48;FD-MS :  $M^+$ =484.

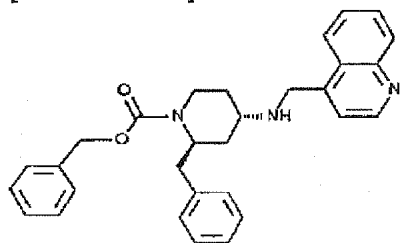
[0143] A start compound for this is prepared as follows.

(2R\* and 4S\*)-2-benzyl-1-(4-chlorophenyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 2j It is made the same. 96 mg (0.56 millimol) It is 58microl (0.795 millimol) first about 4-chlorophenyl acetic acid. You make it react with thionyl chloride. Subsequently, 200 mg (0.468 millimol) You make it react with (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine, and a product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$ =0.39;FD-MS :  $M^+$ =580.

[0144] It is made to be the same as that of the Example 10:(2R\* and 4S\*)-2-benzyl-1-(benzyloxycarbonyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 80 mg (0.142 millimol) () [ 2R\*, ] [ 4S\* ] It is 22 mg (0.57 millimol) about -2-benzyl-1-(benzyloxycarbonyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as colorless oil.

[0145]

[Formula 49]



[0146] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$ =0.43;FD-MS :  $M^+$ =465.

[0147] A start compound for this is prepared as follows.

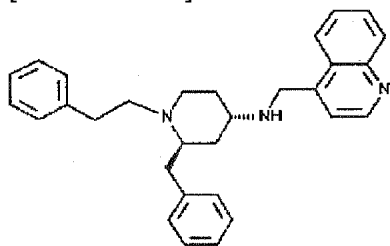
(2R\* and 4S\*)-2-benzyl-1-(benzyloxycarbonyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 67microl (0.468 millimol) Benzyl chloro formate and 72microl (0.515 millimol) Triethylamine It sets at 0 degree and is 200 mg in the methylene chloride of 4 ml (0.468 millimol). It adds in the solution of (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. And mixture is stirred at this temperature for 16 hours.

Subsequently, 34 moremicrol (0.234 millimol) Benzyl chloro formate and 36microl (0.257 millimol) Triethylamine is added and it stirs at a room temperature for 3 hours. Next, it dilutes with a methylene chloride, an organic phase is washed by brine, and evaporation to dryness is dried and carried out on magnesium sulfate. About the obtained oil, they are a methylene chloride / methanol / dark ammonia. (1000:50:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as oil. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.61$ ; FD-MS :  $M^+ = 561$ .

[0148] It is made to be the same as that of the Example 11:(2R\* and 4S\*)-2-benzyl-1-(2-phenylethyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 215 mg (0.494 millimol) It is 77 mg (1.97 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(2-phenylethyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as oil.

[0149]

[Formula 50]



[0150] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.34$ ; FD-MS :  $M^+ = 435$ .

[0151] A start compound for this is prepared as follows.

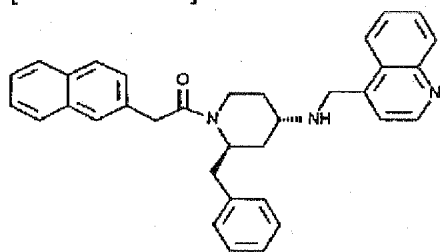
(2R\* and 4S\*)-2-benzyl-1-(2-phenylethyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 209 mul (0.936 millimol) It goes across phenylacetaldehyde in 10 minutes. It sets to a room temperature and is 100 mg in the ethanol of 2 ml (0.233 millimol). (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine, 58 mg (0.702 millimol) Sodium acetate and 44 mg (0.702 millimol) Hydrogenation cyano boron sodium and 67microl (1.17 millimol) Dropping addition is carried out at the solution of an acetic acid. A reaction mixture is stirred at a room temperature for 16 hours. The residue after evaporation in a rotary evaporator is washed by ejection, an organic phase is washed by water and brine in ethyl acetate, and evaporation to dryness is dried and carried out on magnesium sulfate. About the

obtained yellow oil, they are a methylene chloride / methanol / dark ammonia. (2000:50:1) It uses and chromatography processing is carried out on silica gel. The object compound is obtained as oil. TLC : A methylene chloride / methanol / dark ammonia (2000:50:1)  $R_f = 0.33$ ; FD-MS :  $M^+ = 531$ .

[0152] It is made to be the same as that of the Example 12:(2R\* and 4S\*)-2-benzyl-1-(2-naphthyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 160 mg (0.269 millimol) It is 42 mg (1.13 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(2-naphthyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as colorless oil.

[0153]

[Formula 51]



[0154] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.27$ ; FD-MS :  $M^+ = 499$ .

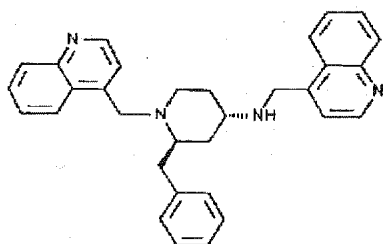
[0155] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(2-naphthyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 6. 105 mg (0.561 millimol) It is 92 microl (0.655 millimol) first about 2-naphthyl acetic acid. It is made to react with 1-chloro-N and an N-2-trimethyl-1-propene-1-amine. subsequently, 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine and 130 mul (0.936 millimol) It is made to react. triethylamine -- \*\* -- A product is given. TLC : a methylene chloride / methanol / dark ammonia (700:50:1) --  $R_f = 0.56$ ; FD-MS :  $M^+ = 595$ .

[0156] It is made to be the same as that of the Example 13:(2R\* and 4S\*)-2-benzyl-1-(4-quinolyl methyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 128 mg (0.225 millimol) It is 34 mg (0.872 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(4-quinolyl methyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as yellow oil.

[0157]

[Formula 52]



[0158] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.45;FD-MS :  $M^+$ =490.

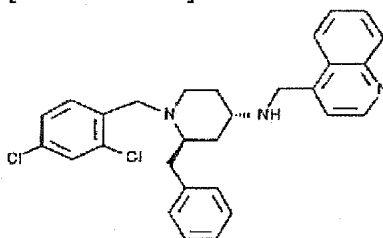
[0159] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(4-quinolyl methyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 11. 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 88 mg (1.4 millimol) Hydrogenation cyano boron sodium, 115 mg (1.4 millimol) Sodium acetate and 134 mul (2.34 millimol) An acetic acid and 294 mg (1.87 millimol) It is made to react with a quinoline-4-carboxy aldehyde, and a product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.33;FD-MS :  $M^+$ =568.

[0160] It is made to be the same as that of the Example 14:(2R\* and 4S\*)-2-benzyl-1-(2, 4-dichloro benzyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 128 mg (0.218 millimol) \*\* (2R\* and 4S\*)-2-benzyl-1-(2, 4-dichloro benzyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine is made to react with the sodium borohydride of 34 mg (0.920 millimol). The bottom-type object compound is obtained as yellow oil.

[0161]

[Formula 53]



[0162] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.25;FD-MS :  $M^+$ =472.

[0163] A start compound for this is prepared as follows.

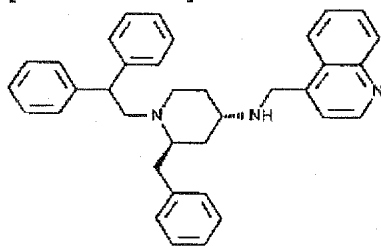
It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(2, 4-dichloro benzyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 11. 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 88 mg (1.4 millimol) Hydrogenation cyano boron sodium, 115 mg (1.4 millimol) Sodium acetate and 134 mul (2.34 millimol) An acetic acid and 294 mg (1.87 millimol) It is made to react with a

quinoline-4-carboxy aldehyde, and a product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.33$ ; FD-MS :  $M^+ = 568$ .

[0164] It is made to be the same as that of the Example 15:(2R\* and 4S\*)-2-benzyl-1-(2 and 2-diphenyl ethyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 170 mg (0.280 millimol) \*\* (2R\* and 4S\*)-2-benzyl-1-(2 and 2-diphenyl ethyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine is made to react with the sodium borohydride of 42 mg (1.12 millimol). The bottom-type object compound is obtained as white form.

[0165]

[Formula 54]



[0166] TLC : A methylene chloride / methanol / dark ammonia (1000:50:1)  $R_f = 0.28$ ; FD-MS :  $M^+ = 511$ .

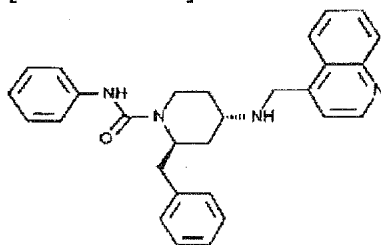
[0167] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(2 and 2-diphenyl ethyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 11. 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 88 mg (1.4 millimol) Hydrogenation cyano boron sodium, 115 mg (1.4 millimol) Sodium acetate and 134  $\mu$ l (2.34 millimol) An acetic acid and 335  $\mu$ l (1.87 millimol) It is made to react with a diphenyl acetaldehyde and a product is given. TLC : A methylene chloride / methanol / dark ammonia (2000:50:1)  $R_f = 0.50$ ; FD-MS :  $M^+ = 607$ .

[0168] It is made to be the same as that of the Example 16:(2R\* and 4S\*)-2-benzyl-1-(phenylcarbamoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 210 mg (0.384 millimol) It is 58 mg (1.54 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(phenylcarbamoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0169]

[Formula 55]



[0170] TLC : A methylene chloride / methanol / dark ammonia (1000:50:1)  $R_f = 0.33$ ; FD-MS :  $M^+ = 450$ .

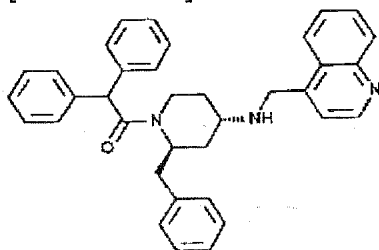
[0171] A start compound for this is prepared as follows.

(2R\* and 4S\*)-2-benzyl-1-(phenylcarbamoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 200 mg (0.468 millimol) ( ) [ 2R\* , ] [ 4S\* ] The solution of -2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 72 mg in the toluene of 5 ml (0.608 millimol) It adds in the solution of phenyl isocyanate, and a reaction mixture is stirred by 100 °C for 2 hours. White suspension is cooled and filtered. 245 The object compound is obtained as a white crystal which has the melting point of 100 °C (decomposition). TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.76$ ; FD-MS :  $M^+ = 546$ .

[0172] It is made to be the same as that of the Example 17: (2R\* and 4S\*)-2-benzyl-1-(diphenyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 235 mg (0.378 millimol) It is 58 mg (1.51 millimol) about 100 °C (2R\* and 4S\*)-2-benzyl-1-(diphenyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0173]

[Formula 56]



TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.49$ ; FD-MS :  $M^+ = 525$ .

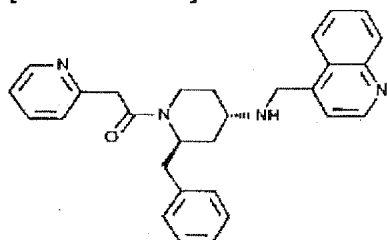
[0174] A start compound for this is prepared as follows.

(2R\* and 4S\*)-2-benzyl-1-(diphenyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 2j It is made the same. 248 mg (1.17 millimol) It is diphenylacetic acid first 128 mg (1.76 millimol) It is made to react with thionyl chloride. Subsequently, 200 mg (0.468 millimol) It is made to react with (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine, and a product is given. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f = 0.45$ ; FD-MS :  $M^+ = 621$ .

[0175] It is made to be the same as that of the Example 18: (2R\* and 4S\*)-2-benzyl-1-(2-pyridyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 180 mg (0.329 millimol) It is 50 mg (1.32 millimol) about 100 °C (2R\* and 4S\*)-2-benzyl-1-(2-pyridyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0176]

[Formula 57]



[0177] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  = 0.28; FD-MS :  $M^+$  = 450.

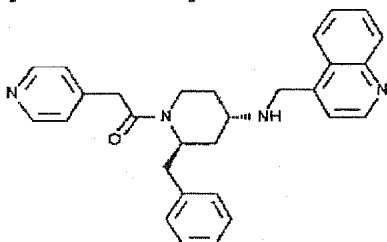
[0178] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(2-pyridyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 4. 200 mg (0.467 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 98 mg (0.561 millimol) 2-pyridyl acetate acid chloride and 143 mg (0.562 millimol) Bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 209  $\mu$ l (1.50 millimol) It is made to react with triethylamine. The object compound is obtained as white form. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  = 0.60; FD-MS :  $M^+$  = 546.

[0179] It is made to be the same as that of the Example 19: (2R\* and 4S\*)-2-benzyl-1-(4-pyridyl acetyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 200 mg (0.366 millimol) It is 55 mg (1.46 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(4-pyridyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0180]

[Formula 58]



[0181] TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  = 0.31; FD-MS :  $M^+$  = 450.

[0182] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(4-pyridyl acetyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 4. 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 98 mg (0.561

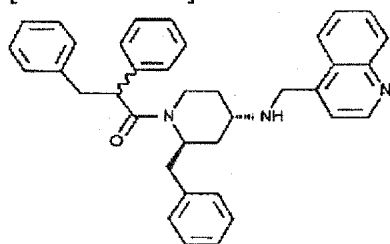


millimol) 4-pyridyl acetate acid chloride and 143 mg (0.562 millimol) Bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 209  $\mu$ l (1.50 millimol) It is made to react with triethylamine. The object compound is obtained as white form. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.56;FD-MS :  $M^+$ =546.

[0183] It is made to be the same as that of the Example 20:(2R\* and 4S\*)-2-benzyl-1-(2, 3-diphenyl propionyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 340 mg (0.535 millimol) It is 81 mg (2.14 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(2, 3-diphenyl propionyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as diastereomer mixture in the form of white form.

[0184]

[Formula 59]



[0185] TLC : A methylene chloride / methanol / dark ammonia (1000:50:1)  $R_f$  =0.37;FD-MS :  $M^+$ =539.

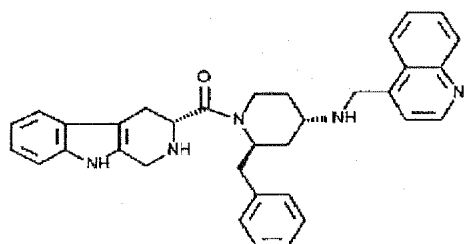
[0186] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(2, 3-diphenyl propionyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 4. 300 mg (0.702 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 190 mg (0.842 millimol) (R, S)-2, 3-diphenyl propionic acid, 214 mg (0.842 millimol) Bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 219  $\mu$ l (1.54 millimol) It is made to react with triethylamine. The object compound is obtained as white form. TLC : A methylene chloride / methanol / dark ammonia (700:50:1)  $R_f$  =0.74;FD-MS :  $M^+$ =635.

[0187] It is made to be the same as that of the Example 21:(2R\* and 4S\*)-2-benzyl-1-[(3S) - (2, 3, 4, 9 - tetrahydro-1H-[3 and 4-pyrid b] Indore-3-IRU) carbonyl]-N-(4-quinolyl methyl)-4-piperidine amine example 2. 197 mg (0.315 millimol) \*\* ( ) [ 2R\*, ] [ 4S\* ] The diastereomer mixture of -2-benzyl-1-[(3S) - (2, 3, 4, 9 - tetrahydro-1H-[3 and 4-pyrid b] Indore-3-IRU) carbonyl]-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 48 mg (1.26 millimol) It is made to react with a sodium borohydride. The bottom-type object compound is obtained as diastereomer mixture in the form of white form.

[0188]

[Formula 60]



[0189] TLC : A methylene chloride / methanol / dark ammonia (350:50:1)  $R_f$  = 0.50; FD-MS :  $M^+$  = 529.

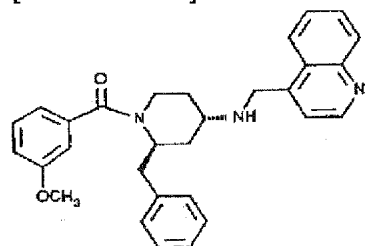
[0190] A start compound for this is prepared as follows.

(2R\* and 4S\*)-2-benzyl-1-[(3S) - (2, 3, 4, 9 - tetrahydro-1H-[3 and 4-pyrid b] Indore-3-IRU) carbonyl]-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 1.97 ml (19.9 millimol) A piperidine 338 in N of 3 ml, and N-dimethyl HORUMI amide mg (0.399 millimol) () [ 2R\*, ] [ 4S\* ] -2-benzyl-1- {-- It adds in the solution of 2-(9-fluorenyl methyloxy carbonyl)-2, 3 and 4, and (3S)-[9-tetrahydro-1H-[3 and 4-pyrid b] Indore-3-IRU] carbonyl}-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. And this mixture is stirred at a room temperature for 2 hours. Subsequently, it is condensed in a rotary evaporator and they are a methylene chloride / methanol / dark ammonia about residue. (2000:50:1) It uses, chromatography processing is carried out on silica gel, and a diastereomer is separated. TLC : A methylene chloride / methanol / dark ammonia (700:50:1) Diastereomer A:  $R_f$  = 0.21; FD-MS :  $M^+$  = 625 ; Diastereomer B:  $R_f$  = 0.13; FD-MS :  $M^+$  = 625.

[0191] It is made to be the same as that of the Example 22: (2R\* and 4S\*)-2-benzyl-1-(3-methoxy benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 230 mg (0.409 millimol) It is 81 mg (2.14 millimol) about \*\* (2R\* and 4S\*)-2-benzyl-1-(3-methoxy benzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine. It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0192]

[Formula 61]



TLC : A methylene chloride / methanol / dark ammonia (1000:50:1)  $R_f$  = 0.26; FD-MS :  $M^+$  = 465.

[0193] A start compound for this is prepared as follows.

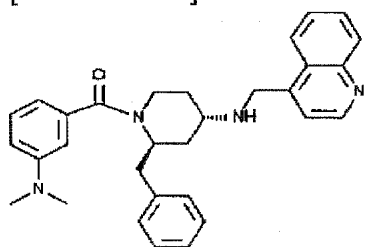
It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(3-methoxy benzoyl)-N-(4-

quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 4. 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 85 mg (0.561 millimol) 3-methoxy benzoic acid and 143 mg (0.561 millimol) Bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 144microl (1.03 millimol) It is made to react with triethylamine. The object compound is obtained as white form. TLC : A methylene chloride / methanol / dark ammonia (1000:50:1) Rf =0.45;FD-MS : M+=561.

[0194] It is made to be the same as that of the Example 23:(2R\* and 4S\*)-2-benzyl-1-(3-N and N-dimethylamino benzoyl)-N-(4-quinolyl methyl)-4-piperidine amine example 2. 225 mg (0.391 millimol) (2R\* and 4S\*)-2-benzyl-1-(3-N and N-dimethylamino benzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 59 mg (1.56 millimol) It is made to react with a sodium borohydride. The bottom-type object compound is obtained as white form.

[0195]

[Formula 62]



TLC : A methylene chloride / methanol / dark ammonia (700:50:1) Rf =0.36;FD-MS : M+=478.

[0196] A start compound for this is prepared as follows.

It is made to be the same as that of the (2R\* and 4S\*)-2-benzyl-1-(3-N and N-dimethylamino benzoyl)-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine example 4. 200 mg (0.468 millimol) (2R\* and 4S\*)-2-benzyl-N-(4-quinolyl methyl)-N-trifluoro acetyl-4-piperidine amine 93 mg (0.561 millimol) 3-N and N-dimethylamino benzoic acid, 143 mg (0.561 millimol) Bis(2-oxo--3-oxazolidinyl) phosphinic acid chloride and 144 mul (1.03 millimol) It is made to react with triethylamine. The object compound is obtained as yellow oil. TLC : A methylene chloride / methanol / dark ammonia (1000:50:1) Rf =0.65;FD-MS : M+=574.

[0197]

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